ANALYSIS OF PROGRAM ACTIVITIES
NATIONAL INSTITUTES OF HEALTH
1955

NATIONAL CANCER INSTITUTE
VOLUME I

NATIONAL INSTITUTES OF HEALTH
PUBLIC HEALTH SERVICE
U. S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

U.S. National Cancer Institute.
"Report of program activities.

PROJECT REPORT FORM

1. National Cancer Institute — INSTITUTE
2. Office of Director — LABORATORY OR BRANCH
3. _____ — SECTION OR SERVICE
4. _____ — LOCATION (IF OTHER THAN BETHESDA)
5. NCI-001 — SERIAL NO.

6. Administration of National Cancer Institute
PROJECT TITLE

7. Dr. J. R. Heller
PRINCIPAL INVESTIGATOR(S)

8. Mr. R. E. Learmouth and Mr. J. M. Hannan
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION
Directs the overall administration of the Institute in conducting research, investigations, experiments and studies relating to the cause, diagnosis, prevention and treatment of cancer; coordinates Institute programs with those of Federal and Non-Federal organizations; edits and manages the Journal of the NCI; participates in determining of policies governing the NIH.

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10. NCI-001
SERIAL NO.

11. BUDGET ACTIVITY

RESEARCH ☐ ADMINISTRATION ☒ X

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

No entries for 12, 13, 14, 15 and 16

PROJECT REPORT FORM

1. National Cancer Institute — INSTITUTE
2. Office of the Director — LABORATORY OR BRANCH
3. Office Services Section — SECTION OR SERVICE
4. — LOCATION (IF OTHER THAN BETHESDA)
5. NCI-002 — SERIAL NO.

6. Variety of administrative management functions in connection with operation of the Institute — PROJECT TITLE

7. Celeste L. Vasco — PRINCIPAL INVESTIGATOR(S)

8. — OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

1. Develops working procedures in areas of travel, overtime, time and leave; prepares special reports, maintains control of equipment on loan; reviews and approves requisitions for supplies, services, printing, shipping

2. Processes papers on all types of personnel actions such as recruitment, promotion, transfer, reassignment and termination for Civil Service and Commissioned personnel, visiting scientists, consultants and contractors.

3. Provides centralized travel services for the NCI which include domestic, foreign and meeting travel; travel in connection with Council and committee members; preparation of vouchers, control of funds, preparation of reports, etc.

4. Provides a typing pool to absorb overflow from all branches and to cover offices in absence of regular personnel.

5. Provides duplicating services for entire Institute with special emphasis on the grants program. Personnel in this unit man tape recorders, or projectors as necessary for meetings within the Institute.

10. NCI-002
SERIAL NO.

11. BUDGET ACTIVITY:

RESEARCH	☐	ADMINISTRATION	☒
REVIEW & APPROVAL	☐	TECHNICAL ASSISTANCE	☐

12. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956.

NONE

13. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

NO ENTRIES FOR 13, 14, 15 and 16.

PROJECT REPORT FORM

1. Cancer — INSTITUTE
2. Office of the Director — LABORATORY OR BRANCH
3. Editorial Office — SECTION OR SERVICE
4. — LOCATION (IF OTHER THAN BETHESDA)
5. NCI- 004 — SERIAL NO.
6. Journal of the National Cancer Institute — PROJECT TITLE
7. Michael B. Shimkin — PRINCIPAL INVESTIGATOR(S)
8. Doris M. Chaney — OTHER INVESTIGATORS
9. PROJECT DESCRIPTION

Review of all manuscripts submitted for publication by the staff of the National Cancer Institute. Preparation of manuscripts from NCI and outside authors for publication in the Journal of the National Cancer Institute. Clearance of manuscripts is required by the Director of the National Institutes of Health to make sure manuscripts are scientifically correct and presented in the best possible form. Publication of the Journal helps solve the urgent and growing problem of prompt and adequate dissemination of scientific knowledge as required by Public Law 410 of the 78th Congress.

PROJECT REPORT FORM (Cont'd.)

10. NCI-004
SERIAL NO.

11. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 OR 1957

None.

12. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

None.

PROJECT REPORT FORM (Cont'd.)

13. NCI- 004
SERIAL NO.

14. PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1955

A total of 332 manuscripts was reviewed, and 1,725 printed pages were published in the Journal of the National Cancer Institute.

15. HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1955.

None.

16. No entries.

17. No entries.

18. No entries.

PROJECT REPORT FORM

1. National Cancer Institute — INSTITUTE
2. Office of the Director — LABORATORY OR BRANCH
3. Cancer Reports Section — SECTION OR SERVICE
4. Bethesda, Maryland — LOCATION (IF OTHER THAN BETHESDA)
5. NCI-005(a — SERIAL NO

6. Weekly, quarterly, and annual (short-form) reports
PROJECT TITLE

7. Mr. Kieley
PRINCIPAL INVESTIGATOR (S)

8. Mr. Callahan
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

These activities provide for the preparation of certain regular reports, as required by the DHEW.

Weekly reports were provided for the Director, NIH, giving brief accounts of items of interest concerning activities of Institute staff members in connection with their respective programs, as well as reports of important developments in intramural and extramural research and other program elements. Fifty-two such reports were prepared.

Reports were prepared at the close of each quarter year on progress in intramural and extramural research and other Institute activities, as requested through Scientific Reports Branch, NIH. Four such reports were prepared.

A short, 5 page annual report of the Institute was prepared for inclusion in the printed annual report of the Public Health Service.

These are continuing activities.

10. CC5-(a)
SERIAL NO.

11.

BUDGET ACTIVITY:

RESEARCH	[X]	ADMINISTRATION	[ ]
REVIEW AND APPROVAL	[ ]	TECHNICAL ASSISTANCE	[ ]

12.

COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 or 1957.

None

13.

IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

None.

NO ENTRIES FOR ITEMS 14, 15 and 16.

PROJECT REPORT FORM

1. National Cancer Institute — INSTITUTE
2. Office of the Director — LABORATORY OR BRANCH
3. Cancer Reports Section — SECTION OR SERVICE
4. Bethesda, Maryland — LOCATION (IF OTHER THAN BETHESDA)
5. NCI-005(b) — SERIAL NO.
6. Special reports, statements — PROJECT TITLE
7. Mr. Kieley — PRINCIPAL INVESTIGATOR(S)
8. Dr. Light, Mr. Kassack, Mr. Callahan — OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

This activity provides for the preparation of non-recurring reports or statements as requested by members of Congress, the Director, NIH, or the Director, NCI. Information for these reports is compiled and prepared in the Section. Several types of reports prepared during year were:

A special report on the NCI extramural research and chemotherapy program for use by Dr. Heller before the Senate Appropriations Committee.

A special statement in connection with hearings on a Bill to authorize a new construction aid program for medical research and education.

A special report on "Advances in Medical Research: Cancer and Man's Environment, and a similar report on tissue culture for use in connection with the 1957 budget presentation by Secretary Folsom.

Assistance in the preparation, including the writing of two sections, of a special report on NCI for a committee of the National Science Foundation in connection with a study of NIH by that organization.

A report on "Research Highlights of 1955," which includes intramural and extramural research progress, for use of Appropriations Committees. This document is submitted for the record in either the House, the Senate, or both. It is also used as reference material during the hearings.

This activity is expected to continue on an irregular basis.

10. NCI-oo5(b)
SERIAL NO.

11.
BUDGET ACTIVITY:

RESEARCH	[X]	ADMINISTRATION	[ ]
REVIEW AND APPROVAL	[ ]	TECHNICAL ASSISTANCE	[ ]

12.
COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 or 1957.

None.

13.
IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH;

None.

NO ENTRIES FOR ITEMS 14, 15, and 16.

PROJECT REPORT FORM

1. National Cancer Institute — INSTITUTE
2. Office of the Director — LABORATORY OR BRANCH
3. Cancer Reports Section — SECTION OR SERVICE
4. Bethesda, Maryland — LOCATION (IF OTHER THAN BETHESDA)
5. NCI-005(d) — SERIAL NO.
6. Research Progress Reports — PROJECT TITLE
7. Mr. Kieley — PRINCIPAL INVESTIGATOR(S)
8. Mr. Kassack, Dr. Light, Mr. Barney — OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

The purpose of this activity is to make available to the Congress regular information on intramural and extramural research progress. Reports are prepared as requested, based on information supplied by various Institute investigators.

During the year, research progress reports were prepared and submitted to Scientific Reports Branch, NIH, on the following subjects:

"Cancer of the Breast"

"The Role of Biochemistry in Cancer Research: Protein Chemistry"

"Leukemia"

This is a continuing activity.

11. BUDGET ACTIVITY:

RESEARCH	[X]	ADMINISTRATION	[ ]
REVIEW AND APPROVAL	[ ]	TECHNICAL ASSISTANCE	[ ]

12. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 or 1957

None.

13. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

None.

NO ENTRIES FOR ITEMS 14, 15 and 16.

PROJECT REPORT FORM

1. National Cancer Institute — INSTITUTE
2. Office of the Director — LABORATORY OR BRANCH
3. Cancer Reports Section — SECTION OR SERVICE
4. Bethesda, Maryland — LOCATION (IF OTHER THAN BETHESDA)
5. NCI-006(c — SERIAL NO.

6. Exchange of information on current progress in cancer chemotherapy
PROJECT TITLE

7. Mr. Kieley
PRINCIPAL INVESTIGATOR(S)

8. Mr. Kassack
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

This activity provides for the issuance, on an irregular basis, of "Current Research in Cancer Chemotherapy," to provide investigators engaged in cancer chemotherapy with an exchange of information on the development and evaluation of chemotherapeutic agents. The total program, of which this is one phase, is sponsored by the National Advisory Cancer Council with the cooperation of the National Cancer Institute, the American Cancer Society, and the Damon Runyon Fund.

During the year, issues Nos. 1, 2, and 3 were prepared, printed under contract, and distributed to the 800 names on the specially prepared mailing list for which addressograph plates were made.

In September Mr. Kassack was detailed to the Cancer Chemotherapy National Service Center, Bldg. 16, in order to handle this and related informational activities on a full-time basis.

This project provides the Committee on Chemotherapy of the National Advisory Cancer Council with information indicating the extent and nature of cancer chemotherapy research both here and abroad.

This is a continuing activity.

10. NCI-006(c)
SERIAL NO.

11.
BUDGET ACTIVITY:

RESEARCH	[X]	ADMINISTRATION	[ ]
REVIEW AND APPROVAL	[ ]	TECHNICAL ASSISTANCE	[ ]

12.
COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 or 1957.

None.

13.
IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

None.

NO ENTRIES FOR ITEMS 14, 15 and 16.

PROJECT REPORT FORM

1. National Cancer Institute — INSTITUTE
2. Office of the Director — LABORATORY OR BRANCH
3. Cancer Reports Section — SECTION OR SERVICE
4. Bethesda, Maryland — LOCATION (IF OTHER THAN BETHESDA)
5. NCI-006(f) — SERIAL NO.
6. Distribution of Publications — PROJECT TITLE
7. Mr. Kieley — PRINCIPAL INVESTIGATOR(S)
8. Mrs. Wall, Mrs. Layton — OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

This activity provides for the bulk distribution of publications on various aspects of cancer research and related activities produced either by the Institute or in cooperation with other Federal or State agencies.

Mailing lists include: State and local health officers; professional organizations; professional schools — medical, dental, public health, and public health nursing; tumor clinics; cancer societies (U.S. and foreign), and health educators in both the United States and overseas.

Bulk mailings, varying in number and type of addresses, totalled 60,000 copies during the year, an increase of 45,000 over the preceding year. Materials relating to the vaginal cytology screening program for uterine cancer accounted for over 14,000 copies. These included reprints of 2 articles, and a new vaginal cytology leaflet, which was prepared to accompany an exhibit on this subject for the medical profession.

"Cancer Services and Facilities in the U. S.," a new directory compiled entirely in the Section, received an initial distribution of 3,400

copies. Other materials distributed included speeches, booklets, pamphlets, Public Health monographs, a nursing manual, and news releases.

This is a continuing activity.

10. NCI-006(f)
SERIAL NO.

11.

BUDGET ACTIVITY:

RESEARCH	[X]	ADMINISTRATION	[ ]
REVIEW AND APPROVAL	[ ]	TECHNICAL ASSISTANCE	[ ]

12.

COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 or 1957.

None.

13.

IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

None.

NO ENTRIES FOR ITEMS 14, 15 and 16.

PROJECT REPORT FORM

1. National Cancer Institute — INSTITUTE
2. Office of the Director — LABORATORY OR BRANCH
3. Cancer Reports Section — SECTION OR SERVICE
4. Bethesda, Maryland — LOCATION (IF OTHER THAN BETHESDA)
5. NCI-007 — SERIAL NO
6. Exhibits, films, slides — PROJECT TITLE
7. Mr. Kieley — PRINCIPAL INVESTIGATOR(S)
8. Mrs. Wall, Mrs. Layton — OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

This activity provides for the production and distribution of audio-visual materials on the various aspects of Institute research for professional audiences.

EXHIBITS -- A new NCI exhibit was designed for the medical profession showing the importance of the cytologic test as a diagnostic aid for the early detection of uterine cancer. The first showing was at the annual meeting of the American Medical Association in June. A leaflet to accompany the exhibit was also prepared in the Section and printed by GPO. A new exhibit for lay audiences, "Cancer -- Where We Stand Today," was also designed and shown at several meetings following its initial display at the New York State Health Conference, Lake Placid. The exhibit, "Half of All Cancer Involves Sites Accessible to Direct Examination" (for professional audiences), and the environmental respiratory cancer exhibit continued in use.

FILMS -- "Lung Cancer: The Problem of Early Diagnosis," was shown at film festivals at Venice, Italy, and Edinburgh, Scotland, through arrangements with the United States Information Agency. This film also received the 1955 Golden Reel Recognition of Merit award, presented by the Film Council of

America for the best film in the medical sciences category. In addition, the Lung Cancer film and another in the professional series on cancer diagnosis, "Oral Cancer: The Problem of Early Diagnosis," were approved by the American College of Surgeons. All six films in the diagnostic series, as well as "Breast Self-Examination" (for lay women), and "Challenge: Science Against Cancer" (for high schools and lay audiences) continued to be shown.

SLIDES -- The slide file is maintained for use of the Director and other staff members in the presentation of statistics or other visual aid material to augment speeches before professional or lay groups. New slides are added and older ones revised or deleted to meet requirements.

A photograph file is also maintained in this activity for use of writers of the Section or newspaper and magazine writers requesting such material. New photos are added as the need arises.

10. 007
SERIAL NO.

11.
BUDGET ACTIVITY:

RESEARCH	[X]	ADMINISTRATION	[ ]
REVIEW AND APPROVAL	[ ]	TECHNICAL ASSISTANCE	[ ]

12.
COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 or 1957.

None.

13.
IF THIS PROJECT RESEMBLES, COMPLEMENTS OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

None.

NO ENTRIES FOR ITEMS 14, 15 and 16.

PROJECT REPORT FORM

1. National Cancer Institute — INSTITUTE
2. Office of the Director — LABORATORY OR BRANCH
3. Cancer Reports Section — SECTION OR SERVICE
4. Bethesda — LOCATION(IF OTHER THAN BETHESDA)
5. NCI-008(a) — SERIAL NO.

6. Speeches, articles, releases to the press
PROJECT TITLE

7. Mr. Kieley
PRINCIPAL INVESTIGATOR(S)

8. Mr. Callahan, Miss Drayer, Dr. Light
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

This activity provides the medical profession and its various segments, and the public in general, with information on the program of the National Cancer Institute, developments in basic scientific research, epidemiological investigations, and the constant application of laboratory findings and clinical experience to the cancer problem at the level of the patient.

This is accomplished through the preparation and/or editing and clearance of news releases, speeches, magazine articles and manuscripts for both the lay and professional press.

During the year 2 speeches and 10 articles were prepared for presentation or publication. Both speeches, prepared for the Director, were requested for publication by editors of professional journals. Still pictures in connection with articles were provided as requested. Nine releases to the press, professional journals and science writers, and 3 press summaries of scientific papers scheduled for presentation, were prepared and distributed.

This is a continuing activity.

10. NCI-008(a)
SERIAL NO.

11. BUDGET ACTIVITY:

RESEARCH	[X]	ADMINISTRATION	[ ]
REVIEW AND APPROVAL	[ ]	TECHNICAL ASSISTANCE	[ ]

12. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 or 1957.

None.

13. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

None

NO ENTRIES FOR ITEMS 14, 15 and 16.

PROJECT REPORT FORM

1. National Cancer Institute — INSTITUTE
2. Office of the Director — LABORATORY OR BRANCH
3. Cancer Reports Section — SECTION OR SERVICE
4. Bethesda — LOCATION (IF OTHER THAN BETHESDA)
5. NCI-008(b) — SERIAL NO

6. Statement of the Director, NCI, before House and Senate hearings on appropriations — PROJECT TITLE

7. Mr. Kieley — PRINCIPAL INVESTIGATOR (S)

8. Dr. Light — OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

This activity provides for the preparation of a statement in support of the Institute budget for fiscal year 1957 for the Director's use before House and Senate hearings on appropriations.

This statement includes comments on the major accomplishments of the Institute, and areas of work contemplated during the coming year. Supplementary materials are prepared as requested. These may include special fields of research or related activities worthy of special emphasis, as well as any visual aid materials deemed appropriate to the presentation.

This is a recurring activity for the Section

10. 008 (b)
SERIAL NO.

11.
BUDGET ACTIVITY:

RESEARCH [X] ADMINISTRATION [ ]

REVIEW AND APPROVAL [ ] TECHNICAL ASSISTANCE [ ]

12.
COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 or 1957.

None.

13.
IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

None.

NO ENTIRES FOR ITEMS 14, 15 and 16.

PROJECT REPORT FORM

1. National Cancer Institute — INSTITUTE
2. Office of the Director — LABORATORY OR BRANCH
3. Cancer Reports Section — SECTION OR SERVICE
4. Bethesda, Maryland — LOCATION (IF OTHER THAN BETHESDA)
5. NCI-008(c) — SERIAL NO.

6. Clearance of Non-research papers — PROJECT TITLE

7. Mr. Kieley — PRINCIPAL INVESTIGATOR(S)

8. Mr. Callahan — OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

This activity provides for the clearance of non-research papers and speeches by NCI staff members, in conformance with Service and Department policies and procedures.

Papers or speeches submitted to the Section for clearance are read in the Section for editorial accuracy, style of presentation, clarity, and conformance to policy. Appropriate reviewers are chosen, either in the Institute or in other divisions of the Public Health Service where the area of work is representative of that discussed in the paper or speech. Inter-bureau clearance, if necessary, proceeds concurrently with NCI clearance. The number of reviewers varies depending upon the subject matter and the scope of the discussion. Comments of reviewers, if any, are transmitted direct to the author but are not identified as to source. The author is asked to incorporate comments into the manuscript or state his reasons for rejecting them. This correspondence is then submitted to the Director, NCI, on whose approval the item is forwarded for completion of clearance through the Scientific Reports Branch, NIH. Notification of final clearance is sent to the author through his Branch Chief.

During the year, 54 speeches and papers were processed through the Cancer Reports Section for either presentation or publication, or both.

This is a continuing activity.

10. 008 (c)
SERIAL NO.

11.
BUDGET ACTIVITY:

RESEARCH	[X]	ADMINISTRATION	[ ]
REVIEW AND APPROVAL	[ ]	TECHNICAL ASSISTANCE	[ ]

12.
COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 or 1957.

None

13.
IF THIS PROJECT RESEMBLES, COMPLEMENTS OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

None.

NO ENTRIES FOR ITEMS 14, 15 and 16.

PROJECT REPORT FORM

1. National Cancer Institute — INSTITUTE
2. Office of the Director — LABORATORY OR BRANCH
3. Cancer Reports Section — SECTION OR SERVICE
4. Bethesda — LOCATION(IF OTHER THAN BETHESDA)
5. NCI-008(e) — SERIAL NO.

6. Reference collection
PROJECT TITLE

7. Mr. Kieley
PRINCIPAL INVESTIGATOR (S)

8. Miss Bain
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

The purpose of this activity is to circulate journals, periodicals, press releases and other materials to the staff of the Cancer Reports Section and professional staff members of the Institute, and to maintain reference files of these materials for use as needed by writers of the Section and other Institute staff members.

This is a continuing activity.

10. NCI-008(e)
SERIAL NO.

11. BUDGET ACTIVITY:

RESEARCH [X] ADMINISTRATION [ ]

REVIEW AND APPROVAL [ ] TECHNICAL ASSISTANCE [ ]

12. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 or 1957.

None

13. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

None

NO ENTRIES FOR ITEMS 14, 15 and 16.

PROJECT REPORT FORM

1. National Cancer Institute — INSTITUTE
2. Office of the Director — LABORATORY OR BRANCH
3. Cancer Reports Section — SECTION OR SERVICE
4. Bethesda — LOCATION(IF OTHER THAN BETHESDA)
5. NCI-010 — SERIAL NO.
6. Public Inquiries — PROJECT TITLE
7. Mr. Kieley — PRINCIPAL INVESTIGATOR(S)
8. Miss Speicher — OTHER INVESTIGATORS
9. PROJECT DESCRIPTION

This activity provides for the handling and reply of day-to-day inquiries from the general public.

Inquiries handled during the year approximated 1,750, requiring 506 individual letter replies, 651 form letter replies, 586 telephone calls, and distribution of over 5,105 pieces of informational literature. Requests for information were received from Congressmen, the White House, and various Government agencies; medical and pre-medical students, nurses, doctors, and all levels of students from elementary to college and post-graduate.

This is a continuing activity.

10. NCI-010
SERIAL NO.

11.
BUDGET ACTIVITY:

RESEARCH	[X]	ADMINISTRATION	[ ]
REVIEW AND APPROVAL	[ ]	TECHNICAL ASSISTANCE	[ ]

12.
COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 or 1957.

None

13.
IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

None

NO ENTRIES FOR ITEMS 14, 15 and 16.

PROJECT REPORT FORM

1. National Cancer Institute — INSTITUTE
2. Office of the Director — LABORATORY OR BRANCH
3. Cancer Reports Section — SECTION OR SERVICE
4. Bethesda, Maryland — LOCATION (IF OTHER THAN BETHESDA)
5. NCI-C11 — SERIAL NO

6. Service to the Press
PROJECT TITLE

7. Mr. Kieley
PRINCIPAL INVESTIGATOR(S)

8. Mr. Callahan, Mr. Barney, Dr. Light
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

The purpose of this activity is to accommodate science writers or reporters who regularly call the Section for information in developing news or feature stories, or for statements or comments of staff members relative to a particular development or story on cancer research and related activities.

During the year interviews with Institute staff members were arranged for science writers or reporters representing the following professional or lay magazines and newspapers or wire services:

Reader's Digest, U.S.News and World Report, Toronto (Ontario) Star, Saturday Evening Post, the Washington Post and Times-Herald, and the Evening Star, Washington, D. C. newspapers.

Assistance was given to more than a dozen writers in developing stories for their magazines, newspapers, or news services including those from the Scripps-Howard News Service, Science News Service, the Houston Post, the Buffalo News, the Baltimore Sun, United Press and Associated Press.

Prepared scripts and visual material for two separate talks by the Director on WTTG-TV, one on radiation, the other in behalf of the American Cancer Society's cancer fund drive. Prepared material for two telecasts by

Dr. Watt of the Heart Institute on the importance of early diagnosis of cancer, and chemotherapy of cancer, for broadcast on Station WTTG. Also assisted with arrangements for a tape-recorded interview with Dr. Hueper for Radio Station WINX, Rockville.

This is a continuing activity.

10. NCI-011
SERIAL NO.

11. BUDGET ACTIVITY:

RESEARCH	[X]	ADMINISTRATION	[ ]
REVIEW AND APPROVAL	[ ]	TECHNICAL ASSISTANCE	[ ]

12. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 or 1957.

None.

13. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

None.

NO ENTRIES FOR ITEMS 14, 15 and 16.

PROJECT REPORT FORM

1. National Cancer Institute — INSTITUTE
2. Office of the Director — LABORATORY OR BRANCH
3. Cancer Reports Section — SECTION OR SERVICE
4. Bethesda, Maryland — LOCATION (IF OTHER THAN BETHESDA)
5. NCI-012 — SERIAL NO

6. Publications — PROJECT TITLE

7. Mr. Kieley — PRINCIPAL INVESTIGATOR(S)

8. Mr. Callahan, Dr. Light, Miss Drayer, Mr. Kassack, Miss Gegan, Mr. Barney — OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

"Reading on Cancer - An Annotated Bibliography," prepared by the Section, was published. The 16-page booklet contains 174 entries including books, pamphlets, reports, articles in popular periodicals and professional journals, and other pertinent material.

A brochure on the National Cancer Institute was completed and forwarded to GPO for printing. This booklet describes the Institute and all its activities both intramural and extramural, its place in the national attack on cancer, the magnitude of the cancer problem, and contains photographs selected from both the intramural and extramural activities. It will be distributed to the lay public in reply to requests for information on the Institute, many of which are received in the Section from the general public. The booklet was in the process of publication as the year closed.

Work was begun on copy for a pamphlet which will summarize in lay reading, a technical report, "Iowa State Cancer Morbidity Study," written by NCI statisticians.

Work was begun on a "Cancer Fact Book," This proposed book will cover all phases of cancer research and control, in non-technical language for adult reading and study. It is designed for use at high school level by teachers of science classes, health education, and social sciences, as well as by student groups, science writers, and adult education groups.

This activity is expected to continue, as required.

10. NCI-012
SERIAL NO.

11. BUDGET ACTIVITY:

RESEARCH	[X]	ADMINISTRATION	[ ]
REVIEW AND APPROVAL	[ ]	TECHNICAL ASSISTANCE	[ ]

12. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 or 1957.

None.

13. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

None.

NO ENTRIES FOR ITEMS 14, 15 and 16.

PROJECT REPORT FORM

1. National Cancer Institute — INSTITUTE
2. Office of the Director — LABORATORY OR BRANCH
3. Cancer Reports Section — SECTION OR SERVICE
4. Bethesda, Maryland — LOCATION (IF OTHER THAN BETHESDA)
5. NCI-013 — SERIAL NO.

6. Cooperation with national educational interests, and dissemination of information to promote more interest in the teaching of cancer in high school science classes with the aim of improving science teaching in secondary schools.
PROJECT TITLE

7. Mr. Kieley
PRINCIPAL INVESTIGATOR(S)

8. Dr. Light
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

This activity provides for the National Cancer Institute's practical cooperation with national educational interests mutually concerned over the growing deficit of young people preparing for careers in scientific research. On recommendation of the National Advisory Cancer Council, the Surgeon General awarded a grant of $18,792 to the National Science Teachers Association to conduct a Science Teacher Achievement Recognition (STAR) Program among high school science teachers with the object of improving the teaching of science courses at the secondary school level. This project has three specific aims: 1) to promote more effective and widespread teaching about cancer in high school general science, biology, chemistry, and physics courses to the end that high school students will become better informed and more intelligently aware of the problems and aspects of cancer and more favorably disposed toward realistic practices of control; 2) to provide a mechanism and encouragement for high school science teachers to submit reports of their successful experiences, ideas and unit outlines for teaching about cancer; and 3) to add to the literature that is designed for, or is effective in, the encouragement of high school youth to take those courses that keep the doors open to careers in science and thus to help increase the pool from which future doctors and research scientists in this field can be recruited. Four members of the NCI staff, including Mr. Kieley and Dr. Light of this Section, were named as local advisers to the steering committee of the project.

The Institute, in collaboration with the National Science Teachers Association, sponsored a one-day cancer information institute for high school science teachers in the Washington area and nearby Maryland, Virginia, Pennsylvania, and Delaware. In a program at the Clinical Center a group of 200 teachers heard a description by NCI staff members of experiments and projects useful for high school science classes, and witnessed demonstrations of these experiments in forms which can be reproduced in high schools.

The first-mentioned of the above items is a continuing activity.

10. 013
SERIAL NO.

11. BUDGET ACTIVITY:

RESEARCH	[X]	ADMINISTRATION	[ ]
REVIEW AND APPROVEL	[ ]	TECHNICAL ASSISTANCE	[ ]

12. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 or 1957.

None

13. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

None.

NO ENTRIES FOR ITEMS 14, 15 and 16.

PROJECT REPORT FORM

1. NCI — INSTITUTE
2. CCNSC — LABORATORY OR BRANCH
3. — SECTION OR SERVICE
4. — LOCATION (IF OTHER THAN BETHESDA)
5. 1200 — SERIAL NO.

6. CANCER CHEMOTHERAPY
PROJECT TITLE

7. K. M. ENDICOTT
PRINCIPAL INVESTIGATOR

8. F. L. SCHMEHL, H. W. BOND, J. LEITER, H. BISEL, C. HUTTRER, E. SPIKE
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

The Cancer Chemotherapy National Service Center, National Cancer Institute, National Institutes of Health, as a result of the interest of the Congress and action taken by the National Cancer Advisory Council, has been established to coordinate a cooperative National Program in the field of cancer chemotherapy research. The organizational framework for this cooperative research includes The American Cancer Society, Damon Runyon Memorial Fund for Cancer Research, National Cancer Institute, Atomic Energy Commission, Food and Drug Administration and the Veterans Administration. These sponsoring organizations cooperate through the Cancer Chemotherapy National Committee. This Committee is composed of representatives of the sponsoring agencies, a member at large, and a member from the Pharmaceutical Industry. It serves as the top policy-making group for the entire cancer chemotherapy program. The CCNSC has been designated as the staff organization to implement the National Program as authorized by the Committee. The Center is jointly staffed by the sponsors and constitutes the full-time staff for the National Program. It provides the secretariat functions to the Committee and organizes and operates five technical panels, the Panel on Pharmacology and Biochemistry, the Panel on Screening, the Panel on Clinical Studies, the Panel on Chemistry, and the Coordinating Committee. These panels are responsible for assessing the state of knowledge of the chemical treatment of cancer, seeking promising avenues of approach, evaluating the progress of the National Program, and advising the sponsors, the Committee and the Center on technical aspects of the National Program. The Center also arranges for the dissemination as well as the exchange of research information on cancer chemotherapy. It promotes voluntary cooperation among scientists and renders technical assistance and other services to participating scientists.

(Serial No. 1200)

With funds appropriated to the NCI research grants are made upon the recommendation of the National Advisory Cancer Council, and contracts are awarded, for the isolation and synthesis of new chemicals for trial against cancer, for the screening of such compounds against cancer in animals, for studies on the toxicity and pharmacology of promising compounds, for clinical investigation of some of the most promising drugs in man, for investigations on the manner in which such materials act against cancer cells so that promising drugs may be improved, and for the rapid exchange of information amongst all cooperating investigators.

The following is an outline of program developments during the past year:

Activation of Service Center

In 1955 the Center was established, equipped and staffed. All of the senior staff positions for the Center are now filled.

Laboratory Screening

The contract program is now underway with the following five screening centers: Wisconsin Alumni Research Foundation, Southern Research Institute, Stanford Research Institute, Hazelton Laboratories Inc., and Microbiological Associates Inc. These contracts have been established to provide for the screening of drugs against cancer in animals. Detailed specifications have been drawn up and the five screening centers will screen against sarcoma 180, carcinoma 755, and leukemia L-1210. It is expected that the five contractors will be able to screen approximately 2000 compounds by July 31, 1956. At the same time, an intensive exploration is also being made of tissue culture techniques and these studies are already under way through a cooperative arrangement. The preliminary results of this effort are encouraging and it now seems possible that this technique may offer a pre-screening device which is inexpensive, rapid and at the same time uses very little compound. Plans are also being formulated for an intensive study of human tumors growing in heterologous hosts, of ascites tumors, and of various biological techniques, as new screening tools.

Chemical Synthesis

In this area information is being collected on the major sources of compounds for screening in order to expedite procurement for the screening operations. A number of contacts have already been made and almost 1000 compounds have been received and distributed to the screening centers. Most investigators agree that random screening operations should be continued on a large scale, but insist that there also be an attempt at the selection of compounds along methodical and rational lines. The Chemistry Panel is in the process of developing general principles to guide the selection of compounds and the classes of compounds to be screened. It is expected that many of the compounds have been made before and can be located, but others will have to be synthesized either because the amount available is too small or because the compound has never actually been synthesized before. Preliminary talks are now taking place in an effort to establish contracts for the synthesis of some chemicals.

10. 1200
SERIAL NO.

11.
BUDGET ACTIVITY:

RESEARCH	☐	ADMINISTRATION	☐
REVIEW & APPROVAL	☐	TECHNICAL ASSISTANCE	☒

12.
COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 OR 1957:

American Cancer Society
Damon Runyon Memorial Fund for Cancer Research
Atomic Energy Commission
Food and Drug Administration
Veterans Administration
National Microbiological Institute

13.
IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

(Serial No. 1200)

Pharmacology

Criteria has been developed for the pre-clinical pharmacological workup of new agents. In order to meet immediate problems of providing better pharmacological workup of compounds the Center has entered into an agreement with the Food and Drug Administration. The FDA laboratories are now studying three compounds, namely Thio-Tepa, Myeleran, and CB-1348. FDA expects to handle one or two new compounds each month; this will approximate 20 per year. It is anticipated that the Food and Drug Administration will satisfy immediate program needs for pre-clinical pharmacological studies.

Clinical Studies

Clinical research is exceedingly expensive because of bed costs. Trained manpower is in very short supply, and the techniques of clinical investigations are not as precise as they might be. The Clinical Studies Panel is attempting to deal separately with the major stages of clinical chemotherapy evaluation. These stages may be defined as (1) clinical pharmacology and preliminary human trial, (2) broad spectrum clinical screening, and (3) definitive trial. Guide lines have been developed for use in stage 1 studies. A pilot study is being sponsored in the second catagory of broad spectrum clinical screening. The pilot studies have been started in five centers, all working on a common protocol, and studying nitrogen mustard and Thio-Tepa in breast cancer, lung cancer, melanoma, and Hodgkins disease. An inter-institutional cooperative program in acute leukemia has also been instituted in which Methotrexate and 6-Mercaptopurine are being given definite trial as single agents and in combination.

14. 1200
SERIAL NO.

15. PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1955:

Current Research in Cancer Chemotherapy

Supplement 1	February	1955
Supplement 2	April	1955
Supplement 3	November	1955

16. HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1955:

Biometry and Epidemiology Branch

Summary Report, 1955

Investigations in biometry and epidemiology continue much in the same fields and patterns as planned or initiated during the last year. The programs perforce must be restricted by limitations of available personnel, space, and budget; sources of records and other material for study continue to be developed but, again, progress is slow because of the same factors.

The cooperation of the Connecticut Department of Health allows exploitation of perhaps the most valuable single source of cancer statistics in the world. The computed data on a defined population extend to 1935 and are as complete and as reliable as they can be made at present. It is heartening to be able to substantiate that, in fact, more patients with cancer survive in 1950 than in 1935; the improvement is not attributable to earlier diagnosis and is probably an effect of better treatment of some specific sites, particularly the rectum and colon, and the uterus. The National Cancer Institute should do, on a long-term basis, everything possible to maintain and to develop investigations in this rich area. The general field of survival in cancer is also being studied by tracing the individuals with cancer identified in the ten-city survey of 1947.

Surveys and analyses continue of geographic regions and of certain populations, relative to the occurrence of cancer. It is gratifying to report that the ten-city cancer morbidity survey of 1947 finally appeared as a publication; it represents a milestone in demographic investigations on cancer. The second part of the survey, concerned primarily with comparisons between the 1937 and the 1947 surveys, is in preparation. Also important is a similar survey carried out in Iowa, which adds urban-rural parameters to morbidity data. Other surveys, in various stages of progress, include cancer mortality among Orientals and Indians in the United States, morbidity and mortality among workers exposed to engine exhausts, retired railroad workers, and in Pittsburgh.

High priority continues to be given to studies on lung cancer. An important survey of the smoking patterns in the United States was performed by the Bureau of the Census for the National Cancer Institute. The analysis is in late stages of preparation for publication. The survey allowed testing of models on the relationships between smoking and lung cancer, and showed that data on this subject obtained from special studies are compatible with lung cancer experience observed for the total population. A retrospective investigation on lung cancer and smoking among women has attracted the collaboration of 62 institutions which thus far have contributed 58 such cases and 116 matched controls. A long-term study is being continued on the epidemiology of lung cancer in Pittsburgh, with particular emphasis on the role of roentgenographic coin lesions. An analysis is being conducted for NCI by the National Research Council of the possible association between war gas exposure and of influenza among the veteran population of World War I.

The Branch is interested in extending biometric and epidemiologic investigations in several directions. One is toward studies on a prospective basis of certain clinically defined populations: e.g., cancer is acromegalics and in hypopituitary patients; cancer of the breast in males with prostatic cancer treated with estrogens; cancer in patients implanted with plastic prosthetic devices. Another is toward studies "in depth" of defined general populations, such as in Connecticut and in Pittsburgh.

Michael B. Shimkin

Michael B. Shimkin, M. D.
Chief, Biometry and Epidemiology Branch
National Cancer Institute

Items NCI 050-069

PROJECT REPORT FORM

1. National Cancer Institute — INSTITUTE
2. Biometry and Epidemiology Branch — LABORATORY OR BRANCH
3. Office of the Chief — SECTION OR SERVICE
4. _____ — LOCATION (IF OTHER THAN BETHESDA)
5. NCI-050 — SERIAL NO.

6. Activities during 1955 — PROJECT TITLE

7. Michael B. Shimkin — PRINCIPAL INVESTIGATOR(S)

8. Piero O. Mustacchi, William J. Pendergrast — OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

The activities of the Office of the Chief have included the following:

(1) General planning and direction of the branch scientific program, as detailed in specific reports of activities.

(2) Participation in epidemiology and related activities of the American Cancer Society through (a) chairmanship of Section on Epidemiology, Committee on Growth, National Research Council and (b) chairmanship of Ad Hoc Advisory Research Committee on Lung Cancer of the American Cancer Society.

(3) Planning and collection of end-results in cancer for a program on the subject scheduled for the Third National Cancer Conference, through chairmanship of the Panel on End-results. (With Dr. Pendergrast)

(4) Scientific editorship of the Journal of the National Cancer Institute, since July 1955.

(5) Investigations of certain aspects of the history of cancer, such as transplantation of tumors and cancer knowledge in the 17th century. (With Dr. Mustacchi)

(6) Laboratory studies on the growth rate of pulmonary tumors in mice (with Drs. Polissar, Andervont, Heston), and on the morphology of testicular tumors in mice (with Dr. Andervont).

10. NCI-050
SERIAL NO.

11. BUDGET ACTIVITY:

RESEARCH	[x]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	TECHNICAL ASSISTANCE	[ ]

12. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 or 1957

National Research Council
American Cancer Society

13. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH

UNKNOWN

4. NCI-050
SERIAL NO.

15. PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1955

(1) Shimkin, M. B., Mustacchi, P. O., Crane, E. B. and Wright, W. H.: Lack of carcinogenicity of lyophilized Schistosoma in mice. J. Nat. Cancer Inst. 16: 471-474, 1955.

(2) Shimkin, M. B.: Hodgkin's disease. Mortality in the United States, 1921-1951; race, sex and age distribution; comparison with leukemia. Blood 10: 1214-1227, 1955.

(3) Shimkin, M. B., and Novinsky, M. A.: A note on the history of transplantation of tumors. Cancer 8: 653-655, 1955.

(4) Shimkin, M. B.: Hormones and neoplasia (a review for Horder and Raven "Cancer", scheduled to be published in 1956). (In press)

16. HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1955

NONE

PROJECT REPORT FORM

1. National Cancer Institute — INSTITUTE
2. Biometry and Epidemiology Branch — LABORATORY OR BRANCH
3. Epidemiology Section — SECTION OR SERVICE
4. Pittsburgh, Pennsylvania — LOCATION (IF OTHER THAN BETHESDA)
5. NCI-052 — SERIAL NO.

6. Epidemiology of Cancer of the Lung, Pittsburgh Field Study — PROJECT TITLE

7. Sr. Asst. Surg. C. D. McClure — PRINCIPAL INVESTIGATOR

8. Dr. W. McD. Hammon and Dr. A. Ciocco, Graduate School of Public Health, University of Pittsburgh — OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: (a) To investigate the clinical and environmental circumstances under which representative cases of cancer of the lung occur in a general population and to determine the characteristics which distinguish people who develop the disease from those who escape it. (b) To partially evaluate the mass small film X-ray survey as a case finding tool.

Methods Employed: (a) Personal interview of all cases diagnosed over a period of several years, together with collection of similar data from a control population. (b) Follow-up, through death certification data of survey and non-survey population; and special and detailed follow-up of selected sample of X-ray examinees who had certain lesions, together with a control group who were negative to X-ray.

Major Findings: (a) None in general study, since systematic field work has been deferred because of necessity of prompt follow-up on X-ray survey sample. (b) Many cases of lung cancer have been identified in the X-ray surveyed, among those with both "positive" and "negative" films. To date, however, definite quantitative statements cannot be made because of the inadequate alphabetization of the Survey index file. Time - and labor - consuming correction of this file is necessary before definitive results are possible.

Significance to Cancer Research: (a) Provides basic information regarding pathogenesis and epidemiology of cancer of the lung which cannot be determined in any other way. (b) Provides partial evaluation of mass small film X-ray surveys as a lung cancer case finding tool.

Proposed Course of Project: Continued follow-up of subjects to death, or over a period of several years.

10. NCI-052
SERIAL NO.

11.
BUDGET ACTIVITY:

RESEARCH [x] ADMINISTRATION [ ]

REVIEW & APPROVAL [ ] TECHNICAL ASSISTANCE [ ]

12.
COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 or 1957

Pittsburgh Cancer Register of Biometry Branch will eventually contribute to study.

Epidemiology and Biostatistics Departments of Graduate School of Public Health.

Many local physicians, hospitals and organizations.

13.
IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

Is complemented by Pittsburgh field studies of Biometry Section, NCI.

4. NCI-052
SERIAL NO.

5. PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1955

McClure, C. D.: "Coin" Lesion Patients and Their Need for Follow Up. Three Case Reports From the Pittsburgh and Allegheny County Mass Chest X-ray Survey of 1953." Bulletin of the Allegheny County Medical Society, May 1955.

McClure, C. D.: "The 'Negative' Chest Film." Bulletin of the Allegheny County Medical Society, January 1, 1955.

16. HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1955.

NONE

PROJECT REPORT FORM

1. National Cancer Institute
INSTITUTE

2. Biometry and Epidemiology Branch
LABORATORY OR BRANCH

3. Epidemiology Section
SECTION OR SERVICE

4. New York City
LOCATION (IF OTHER THAN BETHESDA)

5. NCI-053
SERIAL NO.

6. Cancer in a Closed Population
PROJECT TITLE

7. Med. Dir. A. G. Gilliam and B. K. Milmore
PRINCIPAL INVESTIGATORS

8. NONE
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objective: Primary objective is to measure risk of death from all causes, but more particularly from cancer of the lung, in a closed population excessively exposed to gasoline and diesel engine exhaust fumes.

Methods Employed: Analysis of employment records of about 60,000 men employed between 1906 and 1953; determining causes of death in those dead; and comparing death rates in this population with that for other men in the same city.

Major Findings: Age adjusted relative frequency comparisons suggest that lung cancer might be excessive in this group. However, exact measures of risk await computation of person-years at risk, which cannot be anticipated for another year.

Significance to Cancer Research: Besides providing information regarding risk to cancer of the lung, material should permit contribution to methodology needed in studying industrial groups.

Proposed Course of Project: Tracing causes of death is about 95% complete and has reached the point of uneconomical returns. Causes of death have been coded according to the International List in use at time of death. Death data to be used for computing deaths expected in study group, by broad cause, have been assembled. The necessary rates await completion of appropriate population estimates. The coding of employment records for transfer to IBM cards, necessary for computation of person-years at risk, will commence shortly.

PROJECT REPORT FORM (Cont'd)

10. NCI-053
CLRT'S NO.

11. BUDGET ACTIVITY:

RESEARCH [X] DMINISTRATION [ ]

REVIEW & APPROVAL [ ] TECHNICAL ASSISTANCE [ ]

12. CONVERTING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 or 1957

The Vital Statistics Division of nearly every State Health Department and of several foreign countries.

The Tabulating Unit of NIH will key-punch the coded data and prepare requested tabulations.

13. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

NONE KNOWN

NO ENTRIES FOR NUMBERS 14, 15 and 16

PROJECT RECORD FORM

1. National Cancer Institute
INSTITUTE

2. Biometry and Epidemiology Branch
LABORATORY OR BRANCH

3. Epidemiology Section
SECTION OR SERVICE

4.
LOCATION (IF OTHER THAN BETHESDA)

5. NCI-054
SERIAL NO.

6. Epidemiology of Leukemia and the Lymphomas
PROJECT TITLE

7. Surg. William A. Walter, Jr.
PRINCIPAL INVESTIGATOR(S)

8. None
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: (a) To determine broad selective factors governing the distribution of leukemia and the lymphomas as measurable through analysis of mortality data. (b) To describe the clinical and environmental factors surrounding the development of these diseases in a general population and to determine the broad characteristics of persons who do and who do not develop the disease.

Methods Employed: (a) Detailed analysis of available mortality statistics regarding the trends and age, race, sex and geographic distribution of leukemia in the United States. (b) By personal interview to obtain comprehensive epidemiological information from representative cases occurring in a definable population for comparison with suitable controls.

Major Findings: (a) Although the portion of this project dealing with an analysis of mortality statistics has not reached completion, some preliminary observations may be noted. (1) Age and sex adjusted mortality rates indicate a lower incidence in southern states as opposed to northern states for both white males and females. Non-white data have not been analyzed in this respect at this time. (2) No significant differences in the white male mortality rates age 0-14 years have been observed between states which have significantly high or low white male leukemia death rates. (b) Field work originally instituted in Buffalo was discontinued because of resignation of officer assigned.

Significance to Cancer Research: Provides clinical and epidemiological data from a general population - as opposed to highly selected individual hospital experience - that is basic to understanding of factors governing occurrence of leukemia in people.

Proposed Course of Project: Complete in FY 57 reports of present analysis of mortality data, and reactivate field study if locale offering good prospects of completion of field study can be found.

10. NCI-054
SERIAL NO.

11. BUDGET ACTIVITY:

RESEARCH [X] [ ]

REVIEW & APPROVAL [ ] TECHNICAL ASSISTANCE [ ]

12. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 or 1957

NONE

13. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

NONE KNOWN

NO ENTRIES FOR ITEMS 14, 15 and 16.

PROJECT REPORT FORM

1. National Cancer Institute — 2. Biometry and Epidemiology Branch
INSTITUTE — LABORATORY OR BRANCH

3. Epidemiology Section — 4. — 5. NCI-055
SECTION OR SERVICE — LOCATION (IF OTHER THAN BETHESDA) — SERIAL NO.

6. Studies in Geographic and Racial Distribution of Cancer
PROJECT TITLE

7. Sr. Surg. Robert Lincoln Smith
PRINCIPAL INVESTIGATOR(S)

8. Dr. Clarence Salsbury, Pheonix, Arizona, Sur. William J. Pendergrast,
OTHER INVESTIGATORS Med. Dir. Benno K. Milmore, and Med. Dir. A. G. Gilliam

9. PROJECT DESCRIPTION

Objectives: General: To determine racial and geographic factors influencing risk to cancer. Specific: (a) Study of cancer mortality among Navajo Indians (Smith, Gilliam) (b) Geographic distribution of lung cancer in the United States (Gilliam) (c) Trend of mortality from cancer of the lung in the United States (Milmore) (d) Mortality from cancer in non-white races in the United States and Hawaii (Smith) (e) Geographic distribution and trends of mortality from thyroid diseases and thyroid cancer in the United States (pendergrast).

Methods Employed: (a) Comparison of deaths recorded among the Navajo during 5 years with that expected on the basis of general United States white and non-white age and sex specific rates.

(b, c, d and e) Analysis of United States mortality statistics, published by the National Office of Vital Statistics.

Major Findings: (a) Mortality attributed to cancer of several sites is substantially less among Navajos than among the general United States white and non-white population. However, since both cancer and all other causes of death were less frequently recorded, by the methods employed, than among all Indians; and because of the high proportion of deaths among them either unattended by a physician or attributed to senility, etc., the cancer deficit cannot be regarded as established beyond all reasonable doubt. A paper reporting these findings, as well as differences in other causes of death, has been prepared but not yet submitted for publication.

(b) Marked variation in mortality attributed to lung cancer was demonstrated among the large cities of the United States.

(c) Despite the many limitations of mortality statistics, trends of lung cancer derived from them are believed to reflect adequately trends of this disease as recorded on death certificates.

(d) Interesting differences, in mortality attributed to various cancers among the minor non-white races of the United States and Hawaii, are appearing. However, these data are still incompletely analyzed.

(e) Apparently a crude correlation exists between mortality from thyroid diseases and thyroid cancer. A more critical examination of this point has therefore only recently been instituted.

Significance to Cancer Research: The epidemiological method depends on the demonstration of differences in risk in people with different characteristics, environment, etc. Thus, the results of this project are descriptive and provide information for use in tests of consistency with a variety of theories of cancer causation, as well as leads for further exploration.

Proposed Course of Project: To be continued and expanded in similar direction with other cancers as personnel and facilities become available.

PROJECT REPORT FORM (Cont'd)

0. NCI-055
SERIAL NO.

1. BUDGET ACTIVITY:

RESEARCH	[x]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	TECHNICAL ASSISTANCE	[ ]

2. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 or 1957

Some unpublished basic mortality data obtained from National Office of Vital Statistics on reimbursable basis.

3. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

Studies on geographic distribution of cancer also conducted by Biometry Section and Pathology Laboratory.

14. NCI-055
SERIAL NO.

15. PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1955

Gilliam, A. G.: Mortality attributed to cancer of the lung in the large cities of the U. S. for 1948-49. J. Nat. Cancer Inst. 15: 1307-1312, (April) 1955.

Milmore, B. K.: Trend of lung-cancer mortality in the United States: some limitations of available statistics. J. Nat. Cancer Inst. 16: 267-284, (August) 1955.

16. HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1955.

NONE

PROJECT REPORT FORM

1. National Cancer Institute — 2. Biometry and Epidemiology Branch
INSTITUTE — LABORATORY OR BRANCH

3. Epidemiology Section — 4. — 5. NCI-056
SECTION OR SERVICE — LOCATION (IF OTHER THAN BETHESDA) — SERIAL NO.

6. Research in Epidemiological Method
PROJECT TITLE

7. Medical Directors B. K. Milmore and A. G. Gilliam
PRINCIPAL INVESTIGATOR(S)

8. NONE
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: To examine recorded epidemiological evidence in cancer for its validity and to develop more adequate epidemiological tools for cancer investigation.

Methods Employed: Adaptation and modification of standard epidemiological methods already of demonstrated usefulness in communicable diseases research, and extension and application of these methods to cancer study; including the application of such methods to published data for test of validity of conclusion drawn.

Major Findings: Study of trends of tobacco consumption in the United States indicates that during the period in which pounds consumed per person have increased only 50% the increase in cigarette consumption has been tremendous while other forms of tobacco use have declined. (Milmore)

Study continues of methods of handling occupational data as they might relate to cancer risk. (Milmore and Gilliam)

A method of computing cases or deaths expected from cancer among groups of patients with selected diseases has been developed, concurrently with estimat of the number of cases needed for significant results. (Milmore)

Analysis of trends of mortality from all respiratory diseases indicates that small errors in faulty death certification of lung cancer as other respiratory diseases can theoretically account for a large part, but not all, of the recorded increase in lung cancer since 1914. (Gilliam)

Significance to Cancer Research: Any theories of causes of cancer in humans, from no matter what scientific discipline they come, will remain inadequate until they meet the test of consistency with epidemiological facts. Hence, development of more precise and powerful epidemiological tools is of considerable importance to cancer research.

Proposed Course of Project: To be exploited as new opportunities arise.

14. NCI-056
SERIAL NO.

15. PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1955

Gilliam, A. G.: Some aspects of the lung cancer problem. Military Med. 116: 163-174 (March) 1955.

Gilliam, A. G.: Some epidemiological considerations of cancer of the lung. Paper read at the Inter-American Congress of Radiology, Washington, D. C. April 27, 1955.

Gilliam, A. G.: Trends of mortality attributed to carcinoma of the lung: Possible effects of faulty certification of deaths to other respiratory diseases. Cancer 8: 1130-1136 (Nov.-Dec.) 1955.

Milmore, B. K. and Conover, A. G.: Tobacco consumption in the U. S., 1880 to 1954. In press (January 1956 No.) Agricultural Economic Research.

16. HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956.

NONE

10. NCI-056
SERIAL NO.

11. BUDGET ACTIVITY:

RESEARCH	[x]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	TECHNICAL ASSISTANCE	[ ]

12. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 or 1957

Consultation with Biometry Section.

13. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

NONE KNOWN

PROJECT REPORT FORM

1. National Cancer Institute — 2. Biometry and Epidemiology Branch
INSTITUTE — LABORATORY OR BRANCH

3. Epidemiology Section — 4. — 5. NCI-057
SECTION OR SERVICE — LOCATION (IF OTHER THAN BETHESDA) — SERIAL NO.

6. Stimulation of Epidemiological Research in Non-Service Agencies and Development of Sources of Field Data Suitable to NCI for Answering Specific Epidemiological Questions
PROJECT TITLE

7. Medical Directors A. G. Gilliam and B. K. Milmore and Sr. Surg. Robert Lincoln Sp
PRINCIPAL INVESTIGATOR(S)

8. Surg. William J. Pendergrast and Surg. Piero O. Mustacchi
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: To stimulate the inauguration of epidemiological studies of cancer among people and agencies having pertinent material, the exploitation of which will contribute to an understanding of human cancer; to provide technical assistance in the design of studies, and analysis, of such material; and to explore sources of material directly available to us and suitable for answering specific questions which appear particularly important.

Methods Employed: Through contacts made at meetings of national professional associations, lectures to medical and public health students and exploitation of personal friendships with persons in many agencies, to stimulate and assist in organizing studies of basic epidemiological material not directly available to the Service. By the same means to obtain access to data for our own study.

Major Findings: A study of cancer among a large unrestricted population among which there are social restrictions against use of alcohol, tobacco and coffee was stimulated and designed. Results to date suggest that cancers of several sites fall unequally on this group. Methods of testing the validity of present results have been suggested. (Gilliam)

Cancer epidemiology lectures or seminars conducted at medical or public health schools at Pittsburgh, Johns Hopkins, Virginia, Army Medical Service Graduate School and Naval Medical School. (Gilliam)

Talks to internes and residents, for recruitment of medical and dental officers, at 26 hospitals in Maryland, Virginia and the District of Columbia. (Milmore)

Liaison with National Research Council in connection with a study of the relation of mustard-gas poisoning and influenzal pneumonia in World War I veterans to later development of lung cancer. (Milmore)

Exploring possibilities of studying the possible alteration of susceptibility to cancer among persons with a variety of endocrine disorders and other diseases, with the Veterans Administration and individual hospitals and physicians; and trial use of samples of such case history material. (Milmore, Pendergrast, Mustacchi)

Exploring, through analysis of a trial sample of cases, practicability of using Naval Officer experience in studying the significance of "coin lesions" to cancer of the lung. (Smith)

Exploring suitable sources of material to determine the prevalence and incidence of "coin lesions". One excellent source was found which could have been used to clarify the methodological problems involved, but could not be exploited because of lack of funds. It is probable, however, that the agencies having these data will work them up themselves. (Gilliam, Smith)

Participating in planning for the 1956 National Cancer Conference. (Pendergrast)

Significance to Cancer Research: The future, and broad usefulness, of research in this field depends partly on exploitation of material not directly available to us and on recruitment and training of future workers.

PROJECT REPORT FORM (Cont'd)

NCI-057
PROJECT NO.

BUDGET ACTIVITY:

RESEARCH	[x]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	TECHNICAL ASSISTANCE	[ ]

COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 or 1957

MANY

IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

NONE KNOWN

ENTRIES FOR ITEMS 14, 15 and 16

PROJECT REPORT FORM

1. National Cancer Institute
INSTITUTE

2. Biometry and Epidemiology Branch
LABORATORY OR BRANCH

3. Epidemiology Section
SECTION OR SERVICE

4.
LOCATION (IF OTHER THAN BETHESDA)

5. NCI-059
SERIAL NO.

6. Hypo- and Hyperpituitarism and Cancer
PROJECT TITLE

7. Piero O. Mustacchi and M. B. Shimkin
PRINCIPAL INVESTIGATOR(S)

8. None
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objective: To ascertain whether hyperfunction and hypofunction of the pituitary has an effect on the occurrence of cancer in man.

Methods Employed: Review of literature and collection of clinical cases; comparison of observed with expected rates.

Major Findings: Cases of Sheehan's syndrome or of Simmonds' disease were culled from the literature. A total of 297 women aggregating 2800 person years at risk and 57 men aggregating 360 years were gathered. These had 7 cancers among women and 1 among men. The expected figures were 8.6 among women and 1.0 among men.

Significance to Cancer Research: Hypophysectomy in animals retards development of tumors; it is of obvious interest to ascertain the situation in man.

Proposed Course of Project: The medical literature is being culled for cases of acromegaly, particularly those with autopsy. Acromegaly and hypopituitary case records will be gathered at local hospitals, and in San Francisco and Chicago.

PROJECT REPORT FORM (Cont'd)

10. NCI-059
SERIAL NO.

11.
BUDGET ACTIVITY:

RESEARCH	[x]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	TECHNICAL ASSISTANCE	[ ]

12.
COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 or 195

Hospitals in Baltimore, Chicago and San Francisco.

13.
IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

NONE KNOWN

NO ENTRIES FOR ITEMS 14, 15 and 16.

PROJECT REPORT FORM

1. National Cancer Institute
INSTITUTE

2. Biometry and Epidemiology Branch
LABORATORY OR BRANCH

3. Biometry Section
SECTION OR SERVICE

4.
LOCATION (IF OTHER THAN BETHESDA)

5. 060 NCI
SERIAL NO.

6. Survival Data on Cancer Patients Enumerated in Morbidity Surveys
PROJECT TITLE

7. William Haenszel
PRINCIPAL INVESTIGATOR(S)

8.
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

(A) Objectives: To extend survival information to cover a five year period for newly diagnosed patients enumerated in morbidity surveys. These data will be collated with the experience of cancer registers and of clinical series reported in the literature. The scope of the experience (45,000 cases) will permit systematic examination of such factors as color, sex, age, geographic region, place of treatment, and economic status, in addition to primary site.

(B) Methods Employed: Lists of cancer patients are being searched against death indexes maintained in vital statistics offices. In selected areas hospitals and physicians will also be contacted for further information on patient status and to estimate the loss to follow-up by reliance on vital statistics records only.

(C) Major Findings: Searches against death indexes and vital statistics offices have been completed for Chicago and Dallas and are under way for Pittsburgh and Philadelphia. Of the Chicago and Dallas cancer patients alive one year after date of first diagnosis, 38 percent are known to have died in the subsequent four years. The number of known deaths will be increased when other sources of information are checked.

(D) Significance to Cancer Research: Survival experience of cancer patients is not very well documented. Most series are based on a limited number of cases and worse still, have not been analyzed in a uniform manner and have not included all cases coming into the field of observation. These survival data, when analyzed by standard definitions and methods will provide useful reference bench marks.

(E) Proposed course of this project for the succeeding calendar year: A monograph (or a series of reports dealing with individual sites) will be prepared analyzing the data and relating the findings to other published experience.

PROJECT REPORT FORM (Cont'd)

10. NCI 060
SERIAL NO.

11. BUDGET ACTIVITY:

RESEARCH	[X]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	TECHNICAL ASSISTANCE	[ ]

12. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 or 1957.

State and city departments of health
National Office of Vital Statistics

13. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

Unknown

NO ENTRIES FOR ITEMS 14, 15 & 16

PROJECT REPORT FORM

1. National Cancer Institute
INSTITUTE

2. Biometry and Epidemiology Branch
LABORATORY OR BRANCH

3. Biometry Section
SECTION OR SERVICE

4. _____
LOCATION (IF OTHER THAN BETHESDA)

5. NCI 061
SERIAL NO.

6. Consultation on cancer registers and application of statistical methods to study of cancer in human populations
PROJECT TITLE

7. William Haenszel
PRINCIPAL INVESTIGATOR(S)

8. All professional personnel on Section staff
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

(A) Objectives: To assist other branches of the National Cancer Institute, state and local health departments, and other health agencies by consultation and advice on methodological problems in the maintenance of cancer registers and on the analysis of data collected. This includes the development of statistical tools useful for the analysis of field observations on human populations and their application to specific problems.

(B) Methods Employed: The consultation draws on standard statistical and actuarial techniques and accepted principles for records management, with necessary modifications required for an individual study situation. Many of the problems can be handled by correspondence, but field trips are required in several instances. Consideration must be given to the study objectives of the individual investigator or agency, the existing administrative arrangements and the personnel and financial means at hand to implement the program of operations and studies.

(C) Major Findings: Acting in the capacity of a service organization, the Section primarily assists other investigators in shaping their operations and formulating their findings. Sometimes this assistance is acknowledged in publications by the individuals assisted.

(D) Significance to Cancer Research: Many of the benefits of the consultation program are long-range in nature and consist of setting up record systems and study situations which enlarge the potential study resources of NCI and related organizations. The major activities in the past year are indicated below:

1. Memphis cytology project: advice on record procedures and design of punch card, and plans for the analysis of data collected bearing on the epidemiology of carcinoma in situ and invasional cervical cancer.

2. Collaboration in the analysis of data from the Connecticut cancer register (this collaboration is so extensive that it is reported as a separate project).

3. Consultation to the Oklahoma and Pennsylvania State Health Departments on revision of cancer case reporting procedures.

4. Consultation to Ohio State Department of Health on its studies on occupational differentials in cancer mortality and morbidity.

5. Advice to hospitals on maintenance of cancer registers, a demand stimulated by the American College of Surgeons' program for tumor clinic accreditation.

6. Work on problems in reconciling findings from retrospective and forward studies on the association of smoking and lung cancer.

PROJECT REPORT FORM (Cont'd)

10. NCI-061
SERIAL NO.

11.
BUDGET ACTIVITY

RESEARCH	[X]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	TECHNICAL ASSISTANCE	[ ]

12.
COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 or 1957

Many, as under 9.

13.
IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

The Epidemiology Section of this Branch conducts parallel research

14. NCI-061
SERIAL NO.

15. PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 19

William Haenszel. Epidemiological Tests of Theories on Lung Cancer Etiology Accepted for publication in the January 1956 issue of Public Health Reports.

16. HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1955

Mr. Haenszel was elected Chairman of the Statistics Section, American Public Health Association for 1955-56.

Mr. Haenszel was appointed a member of the Regional Advisory Board of the Biometric Society.

PROJECT REPORT FORM

1. National Cancer Institute — INSTITUTE
2. Biometry and Epidemiology Branch — LABORATORY OR BRANCH
3. Biometry Section — SECTION OR SERVICE
4. — LOCATION (IF OTHER THAN B.S.M.S.D.A)
5. NCI-062 — SERIAL NO.

6. Studies on Cancer in Connecticut, in collaboration with State Health Department
PROJECT TITLE

7. S. J. Cutler and W. M. Haenszel

8. None
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

(A) Objectives: Provide data on cancer incidence, methods of treatment, and end results. Investigate the effect on incidence of epidemiologic factors such as urban environment, nativity, economic status, occupation, diet, and personal habits. Study in detail the inter-relationship between the condition of the patient at diagnosis, the therapeutic course, and the end results.

(B) Methods Employed: Hospitals accounting for 94% of the approved general hospital beds in the state participate in a case reporting and follow-up program administered by the State Health Department.

(C) Major Findings: A comprehensive statistical review of the experience in Connecticut during the period 1935-1951 is contained in a monograph now in press and two completed papers submitted for publication. Several additional papers will be published during the coming year.

The trend in survival rates indicates that the outlook for diagnosed cancer cases is improving. There has been a marked increase in five-year survival rates for cancer of the large intestine, rectum, cervix uteri, corpus uteri, and endocrine glands. Some improvement in survival was observed also for cancer of the larynx, breast, kidney, bladder, and hematopoietic system.

(D) Significance to Cancer Research: Provides basic epidemiologic information regarding the incidence of cancer and data for evaluating therapy in terms of end results.

(E) Future Course of the Project: During the forthcoming year analysis will continue and will include subjects such as:

1. Causes of death among "long term" survivors;

2. Reconciliation of trend data on incidence, mortality, and survival;

3. Probability of developing a second primary cancer;

4. Survival experience of patients that refused treatment to evaluate the "natural history of cancer";

5. Detailed analysis of the relationship of therapy to survival taking into account the reasons for the selection of the prescribed course of therapy in each individual case.

PROJECT REPORT FORM (Cont'd)

10. NCI-062
SERIAL NO.

11. BUDGET ACTIVITY:

RESEARCH	[X]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	TECHNICAL ASSISTANCE	[ ]

12. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 or 1957

13. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

14. NCI-062
SERIAL NO.

15. PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1955

Griswold, M. H., Wilder, C. S., Cutler, S. J., and Pollack, E. S. Cancer in Connecticut, 1935-1951. Monograph published by Connecticut State Department of Health, (in press).

16. HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1955

PROJECT REPORT FORM

1. National Cancer Institute
INSTITUTE

2. Biometry and Epidemiology Branch
LABORATORY OR BRANCH

3. Biometry Section
SECTION OR SERVICE

4.
LOCATION (IF OTHER THAN BETHESDA)

5. NCI-063
SERIAL NO.

6. Study of Mortality and Disability Retirement Due to Cancer Among Railroad Workers
PROJECT TITLE

7. Dr. S. C. Ingraham and William Haenszel
PRINCIPAL INVESTIGATOR(S)

8. Benjamin Carroll
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION: The study is being undertaken in cooperation with the Field Studies Section, Field Investigations and Demonstrations Branch.

(A) Objectives: To determine occupational and other group differentials in the incidence of lung cancer (and other cancer sites) among railroad workers, which can then be used as leads for further detailed investigations (in cooperation with railroad medical departments) to test hypotheses on specific etiological factors.

(B) Methods Employed: A cohort of all working and retired railroad employees with at least 10 years service in the industry as of January 1, 1953 has been established and covers approximately 1,100,000 persons. The Railroad Retirement Board has supplied the investigators with a duplicate set of punch cards describing the population base. Under contract, the RRB has furnished information on deaths in this cohort for the year 1953 and data for 1954 are now being collected.

(C) Major Findings: Data are still being collected and no analysis will be attempted until after two years of results are at hand. The Heart Institute is interested in analyzing the material on mortality for cardiovascular diseases which is being collected.

(D) Significance to Cancer Research: Railroad employees are an occupationally stable group, with their own retirement system. This is an ideal setting in which to attempt investigation of occupational factors and will provide good experience for later handling occupational data collected in Social Security Board operations. Certain railroad employees are known to be exposed

to carcinogenic agents and we have here a direct means of observing the effects. With a defined cohort, holding certain occupational factors constant, it would be possible to supplement the RRB records with collection of additional details on personal histories (in cooperation with railroads) to test association with other factors.

(E) Proposed course of this project for the succeeding calendar year: At least two years mortality experience need to be collected before findings on occupational differentials and mortality can be reported. It is anticipated that mortality and disability retirement experience may be collected over a period of years and that details on specific occupations and exposures to suspected carcinogenic agents may be studied.

PROJECT REPORT FORM (Cont'd)

10. NCI-063
SERIAL NO.

11. BUDGET ACTIVITY:

RESEARCH	[X]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	TECHNICAL ASSISTANCE	[ ]

12. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 or 1957

13. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

NO ENTRIES FOR ITEMS 14, 15 & 16

PROJECT REPORT FORM

1. National Cancer Institute — INSTITUTE
2. Biometry and Epidemiology Branch — LABORATORY OR BRANCH
3. Biometry Section — SECTION OR SERVICE
4. — LOCATION (IF OTHER THAN BETHESDA)
5. NCI-064 — SERIAL NO.

6. Survey of smoking patterns in the United States — PROJECT TITLE

7. William Haenszel and Michael B. Shimkin — PRINCIPAL INVESTIGATOR(S)

8. None — OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

(A) Objective: To describe the tobacco smoking patterns for a representative cross-section of the United States population over 18 years of age; to collate the information on distribution of smoking habits in the population with information on relative lung cancer risks among smokers and nonsmokers provided by special investigations, to see whether they are compatible with the more broadly based information on the epidemiology of lung cancer in the United States.

(B) Methods Employed: The field collection of smoking data in the population was done by the U. S. Bureau of the Census under contract with the National Cancer Institute. Tabulation plans and specifications were drafted by the investigators and furnished to the Bureau of the Census. The NCI investigators analyzed the survey results.

A schedule of relative lung cancer risks reported by special studies was adopted for investigation. This model, when applied to the distribution of smoking patterns in the population, led to certain predictions concerning the distribution of lung cancer in the population with respect to sex, urban-rural residence, race, and major geographical regions. The predictions of the model were compared with the observed facts.

(C) Major Findings: A monograph discussing the smoking survey results is nearing completion. Some marked differences in the percentage of all regular cigarette smokers and heavy smokers (those smoking more than 1 pack of cigarettes daily)

were found when the data were analyzed by age, farm and nonfarm residence, race, and history of military service.

In investigating the model of relative risk among smokers and nonsmokers, the findings predicted by the model with respect to sex ratio, urban-rural ratio, white-nonwhite ratio, and regional variation agreed in general with the relationships observed in cancer mortality and morbidity data and are incorporated in a paper being submitted for publication. They suggest that the associations noted between smoking and lung cancer are not peculiar to the special populations studied and support the generalization of the results of the retrospective and forward studies as being applicable to the total population.

(D) Significance to Cancer Research: Provides one test useful to the interpretation of the reported relationship between smoking and lung cancer.

(E) Proposed course of this project for the succeeding calendar year: It is planned to collect supplemental smoking and residence histories for a sample of U. S. lung cancer deaths (with control data for other causes) to collate with the population data already collected for direct estimation of rates. A study along similar lines is now being conducted by Stocks in Great Britain.

PROJECT REPORT FORM (Cont'd)

10. NCI-064
SERIAL NO.

11. BUDGET ACTIVITY:

RESEARCH	[X]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	TECHNICAL ASSISTANCE	[ ]

12. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 or 1957

None

13. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

NO ENTRIES FOR ITEMS 14, 15 & 16

PROJECT REPORT FORM

1. National Cancer Institute (INSTITUTE) 2. Biometry and Epidemiology Branch (LABORATORY OR BRANCH)

3. Biometry Section (SECTION OR SERVICE) 4. (LOCATION (IF OTHER THAN BETHESDA)) 5. NCI-065 (SERIAL NO.)

6. Cancer Illness in Iowa
PROJECT TITLE

7. William Haenszel
PRINCIPAL INVESTIGATOR(S)

8. Samuel C. Marcus
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION:

(A) Objectives: Provide basic data on cancer incidence, prevalence, and mortality in Iowa. Investigate effect of various factors such as age, sex, geographic area within the state and urban-rural status.

(B) Methods Employed: Information on cancer patients seen during the study year (1950) was obtained from virtually every hospital, clinic, laboratory and physician in the state and in certain areas outside the state which were medical centers for Iowa residents.

(C) Major Findings: The major findings were summarized in the Annual Report for 1954 and in two completed publications. One publication is a technical monograph, and the other a more popular report directed to local health officers, public health nurses and workers in voluntary health organizations.

(D) Significance to Cancer Research: The study contributed data useful for the planning of future studies to provide data bearing on the significance of urban-rural differentials for specific sites.

(E) Proposed course of this project for the succeeding calendar year: It is planned to follow the newly diagnosed cancer cases in the 1950 survey to determine the 5 year survival experience by site for urban and rural areas. A resurvey of Iowa in 1957 or 1958 is under consideration and if undertaken would include occupation and residence histories relative to the interpretation of the observed urban-rural differentials.

PROJECT REPORT FORM (Cont'd)

10. NCI-065
SERIAL NO.

11.
BUDGET ACTIVITY:

RESEARCH	[X]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	TECHNICAL ASSISTANCE	[ ]

12.
COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS; PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 or 1957

The Iowa State Department of Health will cooperate in tracing the 5 year survival experience for cancer patients enumerated in the survey.

13.
IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

None

14. NCI-065
SERIAL NO.

15. PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1955

Haenszel, W., Marcus, S. C., and Zimmerer, E. G. Cancer Morbidity in Urban and Rural Iowa. Accepted for publication as a Public Health monograph.

Zimmerer, E. G., and Haenszel, W. Cancer Illness in Iowa. Multilithed by the U. S. Public Health Service (in preparation).

16. HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1955.

PROJECT REPORT FORM

1. National Cancer Institute — INSTITUTE
2. Biometry and Epidemiology Branch — LABORATORY OR BRANCH
3. Biometry Section — SECTION OR SERVICE
4. — LOCATION (IF OTHER THAN BETHESDA)
5. NCI-066 — SERIAL NO.

6. Statistical Studies of Cancer in Pittsburgh Area
PROJECT TITLE

7. William Haenszel and Dr. Antonio Ciocco (these studies are being undertaken in collaboration with the University of Pittsburgh School of Public Health
PRINCIPAL INVESTIGATOR(S)

8. William Lourie
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

(A) Objectives: To pursue a series of intensive cancer morbidity studies in a single area to yield information on factors contributing to unusual incidence for specified sites. The collation of data obtained by a variety of approaches to the same population base will permit stronger inferences to be drawn from the chain of evidence, open the way to designing detailed studies to test specific hypotheses suggested by the evidence, and make possible methodological contributions to field studies of chronic illness in human populations.

(B) Method Employed: In cooperation with the Pennsylvania State Health Department and Pittsburgh City Health Department, a cancer register is being established. The State Health Department has designated the School of Public Health as its agent for receiving cancer reports from hospitals in Allegheny County. Ultimately it is hoped that the City Health Department will take over the routine register functions. It is planned to supplement these data by collection of additional information from hospital records and by a periodical canvass of physicians in private practice. Work on this phase awaits the passage of a bill permitting the Secretary of Health to designate certain diseases as reportable for study purposes in Pennsylvania.

Plans for the succeeding phases of the Pittsburgh studies remain unchanged. The analyses of tracted morbidity data should supply leads for the design of studies to test specific

hypotheses, which would open the second phase of the project. Such studies would utilize the unique source of information available locally, such as: the "population laboratory" in the Arsenal Health District and 1% city sample, and the resources of the Department of Occupation Health (in the School of Public Health) in gaining access to records of people working in plants in the Pittsburgh area.

(C) Major Findings: It will be another two years before enough reporting experience is accumulated to report systematically on differentials by census tract for various sites.

(D) Significance to Cancer Research: The basic notion of epidemiological studies of a population in depth has never been attempted for cancer on this scale. As mentioned in the objectives, these studies will contribute valuable information on methodology in field studies of chronic illness in human populations.

(E) Proposed course of this project for the succeeding calendar year: See 9A.

PROJECT REPORT FORM (Cont'd)

10. NCI-066
SERIAL NO.

11.
BUDGET ACTIVITY:

RESEARCH	/X/	ADMINISTRATION	/_/
REVIEW & APPROVAL	/_/	TECHNICAL ASSISTANCE	/_/

12.
COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 or 1957

Study being undertaken in collaboration with University of Pittsburgh School of Public Health, Pennsylvania State Department of Health and Pittsburgh City Health Department.

13.
IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

No entries for items 14, 15 and 16

PROJECT REPORT FORM

1. National Cancer Institute — INSTITUTE
2. Biometry and Epidemiology Branch — LABORATORY OR BRANCH
3. Biometry Section — SECTION OR SERVICE
4. — LOCATION (IF OTHER THAN BETHESDA)
5. NCI-067 — SERIAL NO.

6. Statistical Consulting and Research Services — PROJECT TITLE

7. Nathan Mantel and Marvin Schneiderman (now detailed to Cancer Chemotherapy National Service Center) — PRINCIPAL INVESTIGATOR(S)

8. Marguerite T. Wood and Mary Wilkinson — OTHER INVESTIGATORS

9. PROJECT DESCRIPTION: Provision of consultative services in statistical design and analysis of experiments, with associated research in statistical methodology.

(A) Objectives: The primary objective of this section is to provide assistance in the design, interpretation, and evaluation of experiments conducted by researchers at the National Cancer Institute, (and other institutes, on request). This includes referee services for the Journal of the National Cancer Institute and Public Health Reports, and mathematical assistance for development of theoretical models of biological behavior.

(B) Methods Employed: The assistance described above is accomplished using the standard methods of biometry, statistics, and probability, with the necessary modifications required by the problem at hand. Frequently, standard statistical methods are not sufficient to handle the problem on which assistance is being given, and it becomes necessary for the personnel of the section to originate new methods.

(C) Major Findings: As a service organization, this section primarily assists other researchers in making important biological and medical findings, rather than in making such findings directly. Such assistance is frequently acknowledged in the publication of findings of the researchers. Examples of the kind of research problems in which assistance is given are shown below.

Occasionally, the nature of the assistance is such as to warrant co-authorship rather than simple acknowledgement. Those

are shown below. Also, new statistical methods originated in this office to handle certain problems are sometimes important enough to warrant separate publication.

(D) Significance to Cancer Research: The significance of the contribution of this section to cancer research is best illustrated by the problems in which the section has provided statistical assistance. These include:

(a) Studies of anti-leukemic agents with respect to efficacy and toxicity to host;

(b) Studies on the growth of a transplanted tumor;

(c) Establishment of concepts of drug effectiveness and drug damage;

(d) Investigations of possible synergistic combinations of antileukemic agents;

(e) Study of age of host as a factor in tumor chemotherapy;

(f) Studies of genetic factors and exogenous influences in tumor metabolism;

(g) Consultation on the design, development and follow-up of clinical studies of the choice of regimens for the administration of anti-tumor drugs;

(h) Continuing study in the field of tissue culture and in the development of synthetic media for tissue culture;

(i) Studies of red blood cell survival and regeneration in disease and in normal states;

(j) Studies of the occurrence of mammary tumors in mice;

(k) Dose-response phenomena in experimentally induced lung tumors (in mice);

(l) Studies of suturing methods and of the effects of adrenal steroids on the healing of surgical wounds on mice;

(m) Development of methods for enumerating liver nuclei in mice.

PROJECT REPORT FORM (Cont'd)

10. NCI-067
SERIAL NO.

11. BUDGET ACTIVITY:

RESEARCH	[X]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	TECHNICAL ASSISTANCE	[ ]

12. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 or 1957

13. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

While there is no essential duplication of work, parallel statistical consulting services are available at the National Heart Institute, the National Institute of Mental Health, and in the Office of the Director, National Institutes of Health

14. NCI-067
SERIAL NO.

15. PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1955

Goldin, Abraham; Venditti, John M.; Humphreys, Stewart R.; Dennis, Don; Mantel, Nathan; and Greenhouse, Samuel W.: Factors Influencing the Specificity of Action of an Antileukemic Agent (Aminopterin). Multiple Treatment Schedules Plus Delayed Administration of Citrovoran Factor. Cancer Research: Vol. 15, No. 1, pp. 57-61, January 1955.

Goldin, Abraham; Venditti, John M.; Humphreys, Stewart R.; Dennis, Don; Mantel, Nathan; and Greenhouse, Samuel W.: A Quantitative Comparison of the Antileukemic Effectiveness of Two Folic Acid Antagonists in Mice. Journal of the National Cancer Institute, Vol. 15, No. 6, pp. 1657-1664, June 1955.

Goldin, Abraham; Venditti, John M.; Humphreys, Stewart R.; Dennis, Don; Mantel, Nathan; and Greenhouse, Samuel W.: An Investigation Into the Synergistic Antileukemic Action of Amethopterin and 6-Mercaptopurine in Mice. Journal of the National Cancer Institute, Vol. 16, No. 1, pp. 129-138, August 1955.

Hundley, James M.; Mickelsen, Olaf; Mantel, Nathan; Weaver, Ruth M.; and Tabor, Robert L.: Height and Weight of First Grade Children as a Potential Index of Nutritional Status. American Journal of Public Health, Vol. 45, No. 11, pp. 1454-1461, November 1955.

Goldin, A.; Venditti, J. M.; Humphreys, S. R.; Dennis, D.; and Mantel, N.: Factors Influencing the Specificity of Action of an Antileukemic Agent (Aminopterin): Host Age and Weight. Journal of the National Cancer Institute, Vol. 16, No. 3, pp. 709-722, December 1955.

Goldin, A.; Humphreys, S. R.; Venditti, J. M.; Dennis, D.; and Mantel, N.: Growth Studies in Sarcoma 37 in Mice. Journal of the National Cancer Institute (in press, April 1956 publication).

Goldin, A.; Venditti, J. M.; Humphreys, S. R.; Dennis, D., and Mantel, N.: Studies on the Management of Mouse Leukemia (L-1210) with Antagonists of Folic Acid. Cancer Research (in press, December 1955 publication).

Olivier, L. J., and Schneiderman, M.: A Method for Estimating Density of Aquatic Snail Population. Experimental Parasitology (in press, March 1956 publication).

Stohlman, F., Jr., and Schneiderman, M.: Application of the Chromium 51 Technique to the Study of Experimental Hemolysis in the Dog. Journal of Laboratory and Clinical Medicine (in press, January 1956 publication).

16. HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1955.

PROJECT REPORT FORM

1. National Cancer Institute — INSTITUTE
2. Biometry and Epidemiology Branch — LABORATORY OR BRANCH
3. Biometry Section
4. — LOCATION (IF OTHER THAN B THESDA)
5. NCI-068 — SERIAL NO.

6. Cancer Illness in the United States — PROJECT TITLE

7. S. J. Cutler and H. R. Dorn (Office of Biometry, NIH) — PRINCIPAL INVESTIGATOR(S)

8. None — OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

(A) Objectives:: Provide basic data on cancer incidence, prevalence, and mortality in the United States. Investigate effect of various epidemiologic factors, such as color, sex, age, geographic region, and economic status.

(B) Methods Employed: Information on cancer patients seen during a specified calendar year obtained from virtually every hospital, clinic, laboratory, and physician in each of ten urban areas surveyed.

(c) Major Findings: Findings on variation in cancer incidence by age, sex, race, marital status, primary site, and histologic type have been published as indicated in listin below. During the past year, analysis of the following aspects of the subject has neared completion:

(1) Geographic variation in cancer incidence;

(2) Relationship of cancer incidence to economic status;

(3) Changes between 1937 and 1947;

(4) Stage at diagnosis;

(5) Consistency of cancer data from various sources.

(D) Significance to Cancer Research: Provides basic epidemiologic information regarding the incidence of cancer.

(E) Proposed course of this project for the succeeding calendar year:
A second monograph will be published during the coming year. Plans for field studies to follow-up on some epidemiologic leads will be worked out in detail. For example, it is of interest to investigate possible reasons for the high incidence of respiratory and urinary cancer in New Orleans.

PROJECT REPORT NO 1 (Cont'd)

10. NCI-068
SERIAL NO.

11.
BUDGET ACTIVITY:

RESEARCH	[X]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	TECHNICAL ASSISTANCE	[ ]

12.
COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 or 1957

Office of Biometry, NIH

13.
IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS) IDENTIFY SUCH RESEARCH:

None

PROJECT REPORT FORM (Cont'd)

14. NCI-068
SERIAL NO.

15. PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1955

Dorn, H. F. and Cutler, S. J. Cancer Illness in the United States. Public Health Monograph No. 29, U. S. Dept. of Health, Education and Welfare, 1955.

Heller, J. R., Cutler, S. J., and Haenszel, W. M. Some Observations on the Epidemiology of Cancer in the United States. Journal of the American Medical Association, (in press).

16. HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1955.

PROJECT REPORT FORM

1. National Cancer Institute — INSTITUTE
2. Biometry and Epidemiology Branch — LABORATORY OR BRANCH
3. Biometry Section — SECTION OR SERVICE
4. _____ — LOCATION (IF OTHER THAN BETHESDA)
5. NCI-069 — SERIAL NO.

6. Retrospective Study on the Association of Smoking and Lung Cancer in Women
PROJECT TITLE

7. William Haenszel and Michael B. Shimkin
PRINCIPAL INVESTIGATOR(S)

8. _____
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

(A) Objectives: To observe whether the association between smoking and lung cancer observed repeatedly for males holds also for females. A study among women will permit estimates of the separate effects of chronological age and duration of smoking, since women of all ages took up smoking in the 1930 decade. Such studies among men are difficult because all men take up smoking at about the same age.

(B) Methods Employed: Histories of smoking and other characteristics are obtained for each diagnosed lung cancer case and two matched controls. The cooperation of 62 institutions has been secured and histories are being collected by persons connected with each institution. The small number of lung cancer cases among women make cooperative study arrangements necessary.

(C) Major Findings: Histories have now been received for 58 women lung cancer cases and 116 matched controls. Very preliminary analysis indicates an excess risk of epidermoid cancer among women smokers. Differences between smokers and nonsmokers do not appear for adenocarcinoma or undifferentiated histologic type, although the numbers are still too small to warrant firm statements on these points.

(D) Significance to Cancer Research: See 9A.

(E) Proposed course of this project for the succeeding calendar year: Collection of data will be continued until an initial goal of 300 diagnosed lung cancer patients is reached.

10. NCI-069
SERIAL NO.

11.
BUDGET ACTIVITY:

RESEARCH	[X]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	TECHNICAL ASSISTANCE	[ ]

12. None
COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 or 1957

13. None
IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

No entries for items 14, 15 and 16

FIELD INVESTIGATIONS AND DEMONSTRATIONS BRANCH

12-Month Period

Report for Period January 1, 1955 Through December 31, 1955

In general, the Branch has continued to operate its multiple activities through the mechanisms of grant programs, direct operation of field investigations and demonstrations, and technical assistance, guidance and consultation to numerous institutions, agencies and organizations interested in the human cancer problem. During the latter part of the year efforts of the Branch were considerably expanded in the field of cytology with the partial development of four new centers where additional research on the cytologic technique for the discovery of early cancer will be undertaken. Additional field studies have been established, particularly in the fields of gastric, oral and lung cancer; the lymphomas and leukemias.

Most of the programs of the Branch have gone forward during the year with the greatest impetus being placed on cytology and other field studies noted above. Brief summaries of the various Branch activities follow below with specific details of activities being included in the project reports appended hereto.

Extramural Grant Programs

Field Investigation Grants

This program, which provides support for studies in the fields of applied research, developmental research and epidemiological research in cancer, was expanded by $300,000 for exfoliative cytology studies through the appropriation made available in July 1955. Under the program a number of grantees have reported significant accomplishments during the year. One such grantee (Airborne Instruments Laboratory) has developed the prototype of an electronic machine which shows definite promise of being able to assist in sorting out negative and positive cervical cytologic smears through the mechanical scanning of such specimens. Such a device, if effective, would markedly reduce the need for trained cytology technicians in a cervical cancer screening program.

Another grantee (DiCarlo, Syracuse University) has made a notable contribution in the field of laryngeal cancer through a study which has resulted in a better understanding of the dynamics of speech production in laryngectomized patients, and development of an improved method for teaching speech after laryngectomy.

Another grantee (Ebeling, University of Maryland), on a small series of cases, has demonstrated that by means of small volume saline washings of the large bowel satisfactory specimens for cytologic study may be obtained. In addition, the study demonstrated that cytologic examination of such specimens holds promise of being a useful method for detecting cancer of the large bowel.

A preliminary report on a gastric and bowel cancer study from a grantee (Macklin, Ohio State University) indicates that close relatives of individuals with such cancers are more apt to have them than the general population.

A considerable impetus was given to the recruitment of medical technologists through a grant awarded to the College of American Pathologists, the American Society of Clinical Pathologists and the Society of Medical Technologists for the production of a recruitment film. The film is excellent and its showing throughout the country has reversed the downward trend which has existed for a considerable period of time in the recruitment of medical technologists.

Continued support has been provided in the field of diagnostic test development but a satisfactory test has still to be developed.

Increased support has been provided several grantees to carry out additional studies on the usefulness of the cytologic technique for the discovery of early cervical cancer and cancer of the lung.

Training Grants

This program, now in its eighth year of operation, which supports the improvement of cancer instruction in medical, dental and osteopathic schools, was expanded during the year to include the participation of one new 4-year medical school and the increased support of a school which changed from a 2 to a 4-year curriculum. Evaluation of the program by means of the cancer learning test indicates there has continued to be a significant gain in the students' knowledge of cancer as a result of its continuation.

State Aid Program

Funds made available to state health agencies under this program continued at the same level as in the previous year. By and large, these funds have been used in the fields of statistics, home nursing care, financial support of cancer clinics, follow-up of cancer patients, and limited laboratory services for indigent patients. With few exceptions the state programs are restricted in scope due to the limited funds available for this purpose and the lack of qualified personnel within the states.

Clinical Traineeships

Under this program 208 graduate physicians were supported in cancer training for periods of time varying from 1 to 12 months. These trainees were located in 75 training centers in 25 states and the District of Columbia. The great majority of these physicians have continued to devote a significant portion of their time to work in some phase of the cancer field upon completion of their training. A larger percentage of the total trainees were supported in pathology training than in previous years because of the scarcity of trained pathologists and the great need for their services in the cancer field.

Radium Loan Program

This program has continued as in past years with radium being provided on loan to 53 hospitals with qualified radiologists located in 29 states and the District of Columbia. This program continues to be in demand as evidenced by the number of requests received which cannot be filled.

Operation of Field Studies

This program is designed to acquire data pertinent to the cause, prevention, diagnosis, treatment and control of cancer through studies of the occurrence of cancer in humans and conducted under field conditions as contrasted to studies of cancer in experimental animals under laboratory conditions.

These studies cover a wide variety of factors which may be related to the causation of cancer, such as the following: Cancer of the breast as related to lactation, pregnancies and hormone therapy; study of etiologic factors in mothers of children with lymphomata; study of occupational histories of a selected group of patients with cancer of the skin; frequency of occurrence of cancer in a group covered by a state-wide unemployment insurance, prevalence of gastric achlorhydria in selected population groups; survival, incidence and prognostic factors in a selected group of gastric cancer patients; clinical and environmental study of mothers of children with malignancy other than hematopoietic; leukemia occurrence in the New England states; geographical incidence of cancer of major sites in upstate New York; cancer occurrence in several selected population groups (Orders of Nuns) in New England; cancer as a cause of death and disability in railroad workers; oral cancer in relation to vitamin deficiency and/or the use of snuff; a study of the cancer experience of non-uranium hard-rock miners in the Rocky Mountain Area; correlation of industrial exposures and the occurrence of lymphoma and leukemia; study of the occupational backgrounds of hospitalized cases of lung and bowel cancer; leukemias and primary bone malignancies in males over the age of 25; cancer occurrence in uranium miners of the Colorado Plateau; the incidence of respiratory cancer among World War I veterans in relation to their smoking habits; the occurrence of cancer among personnel employed in the manufacture of cigarettes; frequency of occurrence of lung cancer among selected occupational groups of civil service personnel; cancer among selected railroad workers; survey of cancer mortality in West Virginia; geographic distribution of respiratory cancer mortality in 15 selected states; cancer experience in personnel employed in bath houses at Hot Springs, Arkansas; cancer experience in community population exposed to unusual radon gas concentration; a study of lymphoma cases treated in a selected hospital in New England, including observations on patients and records; cancer incidence in a population of 5,000 persons examined periodically; cancer incidence in selected population groups in Alabama; etiology of lung, laryngeal, and bladder cancer in New Orleans, Louisiana; relationship of cancer occurrence and socio-economic factors; geographic and environmental factors in cancer mortality in Washington County, Maryland; possible effect of atomic fall-out as reflected in vital statistics; environmental exposure

and medical history, with emphasis on pregnancy-time, of mothers of leukemic children; geographic distribution of cancer in the United States; correlation of thyroid disease and breast cancer; and evaluation of death certificate reliability as source of environmental cancer information.

Some of the above-mentioned studies are of a long range nature which have been continued from the previous year but have not progressed to the point where the data secured will permit valid conclusions to be drawn. The search for new knowledge relative to the occurrence of cancer in humans and environmental factors which may have a bearing on its development has been sharply accelerated during the past year through the establishment of a number of new studies. Among these are those previously mentioned and having a bearing on oral cancer, gastric cancer and the geographic distribution of cancer.

Other field studies are concerned with the search for cancer diagnostic or screening tests and procedures. Among these are the following: Changes in blood as a method of diagnosis in cancer of human beings; the development and evaluation of general cancer diagnostic tests, exclusive of cytology, relating to biochemical and immunologic procedures; evaluation of the Penn Test; electrophoresis and fluorescence of white blood cells as a possible leukemia diagnostic or screening test; evaluation of tubeless gastric analysis as a screening test for gastric cancer; and studies of vaginal cytology as a means of cancer case-finding in selected population groups.

In vaginal cytology efforts have been continued at Memphis in order to screen as large a segment of the female population as possible. Over 100,000 women have been examined cytologically at least one time. Results to date indicate that vaginal aspiration and cytologic interpretation of the smear will uncover about 8 cancers per 1,000 women so examined.

The development and preliminary organization of additional cervical cytology studies in Madison, Wisconsin; Louisville, Kentucky; Columbus, Ohio; Washington, D.C.; and San Diego, California was undertaken during the last half of the year. These studies will reveal data bearing on such questions as the natural history, course and fate of carcinoma-in-situ, age specific prevalence and incidence rates for the in-situ lesion as well as invasive cancer; the reproducibility of the cytologic examination of vaginal aspirates in additional geographic locations; limitations and requirements of vaginal cytology as a screening device, and the possible application of the cytologic technique to other sites of cancer.

During the year the Branch completed a cytologic screening for cervical cancer of NIH female employees who volunteered to participate in the field study. Initial results indicate that four cervical cancers were uncovered in approximately 1,150 volunteers so examined. It is planned to rescreen the same individuals at yearly intervals.

Other field activities of the Branch are related to the field of cancer nursing. Considerable effort has been made to develop a program leading toward the integration of cancer instruction in the basic and

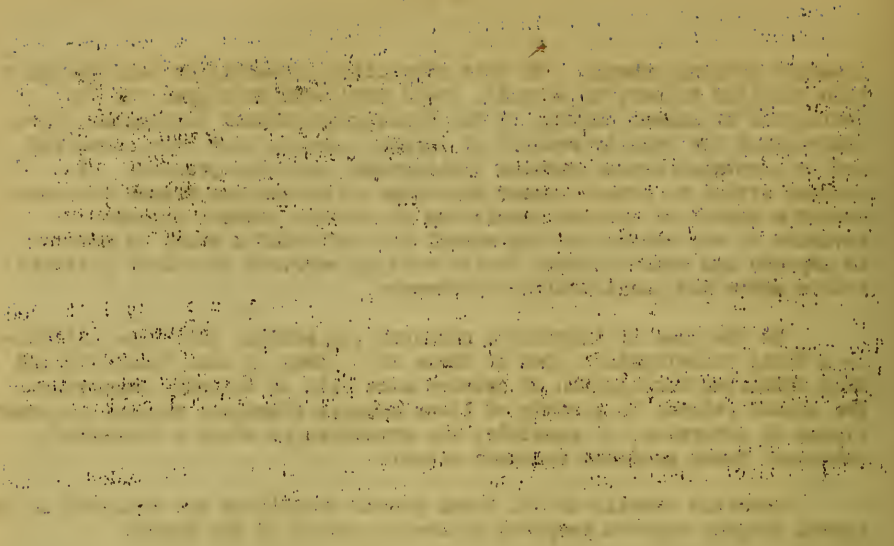
advanced nursing schools. In this connection consultation services have been provided to nursing schools, tools have been developed for the evaluation of cancer nursing in the basic professional curriculum, work conferences for faculty members of nursing schools have been conducted and an annotated cancer nursing bibliography has been prepared. In another effort to extend cancer knowledge to nurses the Branch has conducted a number of nursing institutes in various states, prepared a revision of the cancer nursing manual and initiated a study of methods to improve and extend public health nursing services to cancer patients within state and local health departments.

In the area of laboratory research two studies have been initiated by a field investigator. One of these is a study of neck tumors in AKR mice following inoculation of newborn mice with AK leukemic supernates. The second relates to a study of liver mitotic stimulant present in tumor tissue to determine, if possible, the mechanism by which a localized malignant tumor produces systemic effects.

Specific details of all these Branch activities are included in the annual project reports prepared by section heads of the Branch.

Raymond F. Kaiser, M.D.
Chief, Field Investigations
and Demonstrations Branch

NC-FIDB
2/1/56



1. National Cancer Institute — INSTITUTE
2. Field Investigations and Demonstrations Branch — LABORATORY OR BRANCH
3. Grants Section — SECTION OR SERVICE
4. — LOCATION (IF OTHER THAN BETHESDA)
5. 100 — SERIAL NO.

6. Field Investigation Grants — PROJECT TITLE

7. N. B. Hon, M.D. — PRINCIPAL INVESTIGATOR(S)

8. R. F. Kaiser, M.D. — OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

A. OBJECTIVES

This activity provides funds for the support of projects in field and developmental research, in the evaluation of new and modification of known diagnostic and case-finding procedures and technics, in community studies and surveys of racial and population groups and pilot studies. The primary purpose being to detect cancer in man at the earliest possible stage of the disease when it is possible to effect a cure or to materially extend the span of life.

B. METHOD OF APPLICATION

Through this program working arrangements have been made with many of the medical educational institutions, public and philanthropic and private organizations throughout the country. The Cancer Control Committee and the National Advisory Cancer Council each meet three times each year to consider and recommend action on these grants.

C. MAJOR FINDINGS

During the calendar year 1955 there were 140 grant applications totaling $2,368,126 considered by the Cancer Control Committee and the National Advisory Cancer Council. Of this number 71 grants totaling $1,281,067 were new; 59 grants totaling $903,222 were continuation or old grants; 10 grants totaling $183,837 were supplemental and grants deferred from the previous year.

Of the 140 applications submitted 90 grants totaling $1,377,413 were approved. Of this number 31 grants in the amount of $472,282 were new studies; 54 grants totaling $839,393 were continuation of studies already underway; 5 grants in the amount of $65,738 were for supplemental or deferred grants.

The most significant accomplishments during the year have been in 5 major areas of study: (1) Cancer diagnostic tests, (2) Professional education, (3) Genetics, (4) Rehabilitation, (5) Clinical investigation.

It has been recognized that with the establishment of the reliability of exfoliative cytology as a diagnostic test for cancer a more rapid method of examination of cells than is now possible with the limited trained personnel available will be necessary. This is particularly true if the test is to become a screening device. To determine the feasibility of developing an instrument that would provide a rapid method of examination, a project was undertaken (Airborne Instruments Laboratory) to develop an instrument that would measure, record and tabulate the characteristics necessary to distinguish between normal human vaginal and cervical cells and cancer cells of the same site. This was believed to be possible by measuring mechanically (by means of a scanning and mechanical stage control mechanism, and electronic computer and control circuits for measuring optical density) (1) the mean diameter of the nucleus, (2) the mean diameter of the cell, (3) density of the nucleus stain and (4) the staining reaction of the cytoplasm. In order to determine standards for the construction of a cytoanalyzer the cells of 200 vaginal and cervical smears from 200 persons have been examined manually. The original test model machine has been constructed on the basis of the results of 200 slides examined. The development of the cytoanalyzer has reached the stage that it operates sufficiently satisfactorily to warrant a practical trial. The next step in the development is the testing of the instrument under field conditions which is scheduled for June 1956. A second model with the latest improvements will be constructed for trial in the Cytology Field Study now in progress at Memphis, Tennessee. The data obtained here is necessary to establish definitive design requirements of a production stage model and to determine its effectiveness under routine field conditions. Even with the performance of this machine to date it is expected that the program of cytology could be extended to many more people than is now possible.

The study of cellular acid phosphatase in gastric mucosal cells and acid phosphatase in gastric juice in normal and cancerous stomachs as a means of determining cancer of the stomach is in the process of investigation (Sleisenger). This is the only study of this type being undertaken at the present time. Thus far in the study no significant difference has been shown. However, it is expected that in vivo specimens which have not been possible to date may answer the question.

A notable contribution has been made in the rehabilitation of laryngectomized individuals through the production of a film "Teaching of Speech After Laryngectomy" (Di Carlo, Syracuse University). This film is based on a recent study of the physiology of speech also supported by a grant, which concerned dynamics of speech, breath control, rythmical movement of normal and laryngectomized people. A great amount of confusion has existed in the different methods used in teaching speech to this type of individual. Authorities agree that as a result of this study and the production of this film much of the confusion has been or will be overcome. In addition this method decreases the time required in learning to speak and greatly reduces the fear of patients for this type of operation when appraised of the possibility of being able to speak in a relatively normal manner.

The problems that exists in the studies relating to potential environmental carcinogens can only be solved by the cooperation and mutual understanding of all parties concerned. The recently held environmental cancer conference gives graphic proof that this cooperation is possible and practical. Representatives from industry, directors of research projects, key personnel from medical schools concerned with industrial medicine and National Cancer Institute personnel joined in a two day long discussion of the problems that exist, those most fruitful for investigation and suggested methods of procedure. Additional meetings dealing with specific areas hold the potential of grant returns in the investigations to be done in the entire field of environmental cancer.

During the past 12 months progress has been made on the project to develop new and expand known cytologic techniques for diagnosis and study of diseases of the colon (Ebeling). Sixty-four patients have been studied clinically and by exfoliative cytology technique. Small volume saline washings of the large bowel have produced satisfactory specimens for cytology study. Nine pathologically confirmed carcinomas of the large bowel beyond the 25 c.m. sigmoidoscope were found by saline washing only. Only one case in the study was not confirmed by cytological examination. The success of this method of detecting cancer of the large bowel has stimulated such an interest in the hospital where the study was conducted that there is a demand on the laboratory for similar services for all body sites. As a result of this interest, exfoliative cytology has become an established and reliable technique in the hospital and medical school. Article to be published, entitled, "Demonstration of Malignant Cells Exfoliated from the Proximal Colon".

10. SERIAL NO.

It is generally recognized that there is an urgent need for medical technologists in order to maintain present standard of hospital and private medical laboratory operations. In order to improve this situation a nation wide program of medical technologist recruitment has been undertaken partially supported by these grant funds under the sponsorship of the American Society of Clinical Pathologists, the College of American Pathologists and the Society of Medical Technologists directed by the National Committee of Careers in Medical Technology. The recruitment program has been in operation for two years and plans have been made to continue it on a more intensive and broader basis for a total of six years.

An estimated 24,000,000 young people between the ages of 14 and 24 years of age are the target audience for the recruitment effort. After two years of operation approximately 5,000,000 of this audience have read about the program in lay publications; 250,000 have been appraised of the program in professional publications at both the national and local level. The principal working tool of the Committee has been the recruitment film prepared specifically for this program and telecasts. One hundred sixty-seven films have been distributed to all of the 48 States. The films have been shown 2124 times during the past year to an estimated audience of 75,000 students and in addition to a large number of science classes and "Science Fairs" over the country. The film has been shown on 105 of the nations television stations. A number of foreign countries have expressed interest in the film and prints have been loaned to several of them. The results of the program to date indicate a reversal of the decreasing interest in this profession to one of growing interest. This is judged in part by a substantial increase in the number of transcripts submitted to the schools of medical technology during the first half of 1955. If this continues at the same rate the number will be about one-third more than for any similar period in the past.

Inheritance of gastric cancer has been under study for the past two years in an attempt to find out if there are genetic factors for gastric cancer in man (Macklin). Family histories of patients with pathologically diagnosed gastric and bowel cancer have been assembled and studied to determine whether there is any significant increase in the amount of gastric and intestinal cancer in these families. The study of both stomach and bowel cancer was to determine if there was an increase in both sites in the relatives of gastric patients, thus suggesting an inherited factor for cancer of the gastro-intestinal tract or whether there is a site specificity as well. It was found that when the initial person had a bowel cancer the odd result was obtained that brothers still had more gastric cancer than expected but only the same amount of bowel cancer that one would find in the general population. In the case of sons of such persons there was more gastric cancer and more bowel cancer than would be expected but the excess in the same kind of cancer was greater. In the case of sisters and daughters of persons with bowel cancer

10. SERIAL NO. 100

they both had bowel cancer in excess, the daughter having more than the sisters. From the study thus far it would appear that there is some localizing factor that makes for the same type of cancer in the close relative rather than cancer of the gastro-intestinal tract in general.

10. SERIAL NO. 100

11. BUDGET ACTIVITY:

RESEARCH ☐ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☒

12. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 or 1957

Numerous medical institutions and teaching centers throughout the country.

NO ENTRIES FOR ITEMS 13, 14, 15, 16

1. National Cancer Institute — INSTITUTE
2. Field Investigations and Demonstrations Branch — LABORATORY OR BRANCH
3. Grants Section — SECTION OR SERVICE
4. LOCATION (IF OTHER THAN BETHESDA)
5. 101 — SERIAL NO

6. Undergraduate Training Grants — PROJECT TITLE

7. N. B. Hon, M.D. — PRINCIPAL INVESTIGATOR(S)

8. R. F. Kaiser, M.D. — OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

A. OBJECTIVES

The objectives of this program are to increase the knowledge of medical students in the field of cancer and develop an awareness of the need and possibilities of its early detection; to coordinate the teaching of cancer in a manner that will give the student a comprehensive concept of the disease; to stimulate an interest in cancer research; to better utilize current knowledge of the disease and to increase the index of suspicion of cancer and at the same time de-emphasize its incurability.

B. METHODS EMPLOYED

Funds are made available to approved medical, dental and osteopathic schools. The maximum amount available to each is $25,000 to 4-year medical and osteopathic schools; $5,000 to 2-year medical schools; $5,000 to dental schools. Application for a grant is made by an institution each year together with a plan of the teaching. These are considered by the Cancer Control Committee and the National Advisory Cancer Council and on approval by the Cancer Council the institution is eligible for payment.

C. MAJOR FINDINGS

This is the eighth year of operation of the program. The total amount of the funds available for distribution for the year 1955 was $2,464,167. There are 131 institutions participating in the program. Of this number 83 are medical schools receiving a total of $2,063,373; one new 4-year medical school became operative during the year; 42 are dental schools and received a total of $229,814 and 6 were osteopathic schools receiving a total of $145,980.

The Annual Coordinators Meeting with representation from all schools was held in October 1955. Administrative and professional teaching aspects of the school programs were reviewed. An excellent program on the statistical, olinical and research aspects of cancer was presented. The Ira T. Nathanson Memorial Lectures, entitled, "The Pursuit of the Unorthodox: Some Observations on Cancer Therapy" was presented at the coordinators meeting and later distributed to all cancer coordinators.

As in the past the value of this program is tested through the project for evaluating cancer learning in medical and dental schools. Fifty-three of the medical schools representing 18,501 students participated in the testing program. This is the largest number of students to take the test in a given year since the testing program was initiated. Thirty-seven dental schools representing 10,920 students took the test. This is an increase of students over past years.

D. SIGNIFICANCE OF THE PROGRAM

The relative standing of every school through all its years of participation as reflected by the testing program was determined. It was noted that any changes in the teaching methods were reflected almost immediately by a change in the standing of the school. In a number of instances the cancer teaching programs have been modified by the Coordinators as a result of weakness in the program detected in this evaluation project. The modification of the teaching program has resulted in significant gains in the students knowledge of cancer, particularly during the last three years. Analyses of methods of teaching reveals that there is no single method which can operate effectively of itself. Each method of the institutes must be considered in terms of how it fits into the total pattern of teaching. The pattern most generally effective at the senior level appears to be one that emphasizes clinical instruction and minimizes lectures.

E. PROPOSED COURSE OF PROJECT

It is proposed to continue the program with a slightly decreased grant to the 4-year medical and osteopathic schools because of an increase in number of schools but no increase in appropriation for the program.

10. 101 PROJECT REPORT FORM (Cont'd)
SERIAL NO.

11.
BUDGET ACTIVITY:

RESEARCH ☐ ADMINISTRATION ☐

REVIEW & APPROVAL ☒ TECHNICAL ASSISTANCE ☒

12.
COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 or 1957.

Approved medical, dental and osteopathic schools throughout the country.

13.
IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

None

14. 101
SERIAL NO.

15. PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1955

R. F. Kaiser - Some Results of the Cancer Teaching Program Journal of Medical Education Vol. 30, No. 11, Nov. 1955

R. F. Kaiser - Results of the Cancer Teaching Program in Dental Schools - Public Health Reports, Vol. 70, No. 1, Jan. 1955

NO ENTRIES FOR ITEM 16.

1. National Cancer Institute — INSTITUTE
2. Field Investigations and Demonstrations Branch — LABORATORY OR BRANCH
3. Grants Section — SECTION OR SERVICE
4. — LOCATION (IF OTHER THAN BETHESDA)
5. 102 — SERIAL NO.

6. Grant-in-aid to States — PROJECT TITLE

7. N. B. Hon, M.D. — PRINCIPAL INVESTIGATOR(S)

8. R. F. Kaiser, M.D. — OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

A. OBJECTIVES

The objectives of this program continue to be the cooperation with official State and local health agencies in the stimulation of cancer control activities at the local level that will provide early diagnosis and treatment of the general population through the utilization of grant and matching funds.

B. METHODS EMPLOYED

These funds are made available to State and Territorial Health Departments on submission of an application for funds and an approved program plan. This activity is processed through the various regional offices. The funds are distributed on the basis of a formula which takes into consideration population, financial need and extent of the cancer problem. Consultation services are made available to the States from the Regional Offices with staff members of the National Cancer Institute providing technical guidance to both the regional office and State, local and non-official agencies on request from the State health departments and Regional Office.

C. MAJOR FINDINGS

The 1955 appropriation for this program was $2,250,000. All of the States and Territories received grant funds. All States now have cancer control programs which vary widely in scope and degree of efficiency. The most serious weakness in the program continues to be the lack of trained technical professional personnel and professional administrative staff who have sufficient time to develop and administer a cancer control program. All official State health agencies received grant funds during the year. The main activities of these

10. SERIAL NO. 102

programs are in the fields of statistics, home nursing care, financial support of diagnostic clinics and detection centers, follow-up of cancer patients, and to a lesser degree participation in environmental cancer studies and laboratory diagnostic service primarily limited to exfoliative cytology for indigent patients.

There has been a slight increase in the number of cancer diagnostic clinics supported from these funds. This support has been chiefly to improve local clinic registers to permit qualification as an approved clinic, a requirement of the American College of Surgeons for approval.

The follow-up of cancer patients and home nursing activities have been the main activities of the nursing personnel in the majority of local health departments. A limited number of States have continued to support a professional educational program for physicians and laboratory technicians and an in-service orientation program for nurses. Most of the lay education is in cooperation with non-official agencies.

D. SIGNIFICANCE OF THE PROGRAM

This program is designed to provide the facility and personnel necessary to find and diagnose cancer and provide for treatment of the disease in the earliest possible stage by utilizing more effectively routine methods and applying the newer techniques that have been demonstrated to be of value.

E. PROPOSED COURSE OF PROJECT

An increased effort will be made to employ additional qualified personnel to increase the number of diagnostic clinics, support local clinic registers, follow-up of cancer patients, evaluation of diagnostic and treatment of patients and make available adequate service to a larger portion of the population.

10. SERIAL NO. 102

11. BUDGET ACTIVITY:

RESEARCH ☐ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☒

12. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 or 1957

State and Territorial Health Agencies

13. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

None

14. 102
SERIAL NO.

15.
PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1955

R. F. Kaiser - Cancer Can Be Controlled - U. S. News and World Report, March 25, 1955.

R. F. Kaiser - A Special Purpose Health Education Program: Breast Self Examination, Public Health Reports, Vol. 70, No. 4, April 1955.

Russell Boles, W. S. Baum, R. F. Kaiser - Cancer Detection in General Practice - Journal of American Medical Association, In Press.

R. F. Kaiser - Cancer Control Activities of the National Cancer Institute - Public Health Reports, Vol. 70, No. 10, Oct. 1955.

R. F. Kaiser - Cancer Program of the National Cancer Institute - In Press.
Mass.Cancer Handbook for Physicians

R. F. Kaiser - Cytology as an Aid to the Diagnosis of Uterine Cancer - Accepted by Journal G-P - In Press.

R. F. Kaiser - Research factors in the Control of Uterine Cancer - Accepted by Public Health Reports - In Press

NO ENTRY FOR ITEM 16

PROJECT REPORT FORM

1. National Cancer Institute — INSTITUTE
2. Field Investigations and Demonstrations Branch — LABORATORY OR BRANCH
3. Office of the Chief — SECTION OR SERVICE
4. — LOCATION (IF OTHER THAN BETHESDA)
5. 103 — SERIAL NO.
6. Radium Loan Program — PROJECT TITLE
7. Dr. R. F. Kaiser and Mrs. M. W. Brunot — PRINCIPAL INVESTIGATOR(S)
8. — OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

A. OBJECTIVE

The program provides radium in various types of applicators and intensities to qualified radiologists in approved hospitals throughout the country for use in cancer therapy.

B. METHODS

Radium is lent to institutions seeking such, within the supply available, on an annual contract basis. The recipient of the loan provides insurance coverage for the radium and supplies an annual report on patients treated. The shipments of radium are handled through the National Bureau of Standards, which also provides for calibration and standardization of the units. These services are provided through an annual contract between the National Cancer Institute and the National Bureau of Standards.

C. MAJOR FINDINGS

Throughout the year 1955 radium was on loan to 53 hospitals in 29 states and the District of Columbia. During the year practically the entire supply of radium has been out on loan.

D. FUTURE OF PROGRAM

It is planned to continue the program at its current level as long as there appears to be a significant need for radium which is reflected by the requests we have been unable to fill.

10. 103
SERIAL NO.

11.
BUDGET ACTIVITY:

RESEARCH [ ] ADMINISTRATION [ ]

REVIEW & APPROVAL [X] TECHNICAL ASSISTANCE [X]

12. National Bureau of Standards
COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 OR 1957

13.
IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS) IDENTIFY SUCH RESEARCH:

NO ENTRIES FOR ITEMS 14, 15, and 16.

PROJECT REPORT FORM

1. Cancer — INSTITUTE
2. Field Investigations and Demonstrations Branch — LABORATORY OR BRANCH
3. Office of the Chief — SECTION OR SERVICE
4. — LOCATION (IF OTHER THAN BETHESDA)
5. 104 — SERIAL NO.
6. Clinical Traineeships Program — PROJECT TITLE
7. R. F. Kaiser, M.D. and Mrs. M. W. Brunot — PRINCIPAL INVESTIGATOR(S)
8. None — OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

(A) Objectives.

To provide training support for graduate physicians in the diagnosis and treatment of cancer.

(B) Methods Employed.

Applications for special cancer training are received from physicians desiring such training who have made themselves acceptable to a qualified training center. Applications are reviewed and final selection of trainees made by a traineeships board composed of National Cancer Institute staff members. The successful candidates are appointed by the National Cancer Institute and paid directly from Bethesda headquarters.

(C) Major Findings.

During the year 206 physicians were supported under this program for periods of time varying from one month to a full year. These trainees were distributed in 75 institutions located in 25 states and the District of Columbia. An effort has been made to increase the number of trainees receiving support in cancer pathology which has resulted in an increase in such trainees. During the year the geographic distribution of trainees has been broadened to cover a greater portion of the Nation.

(D) Future Program.

The extent of this program was reduced during the last half of the year due to an increase in stipend levels for trainees which became effective July 1, 1955. Further reduction in the total number of trainees supported will be necessary unless additional funds are made available.

PROJECT REPORT FORM (cont'd)

10. I04
SERIAL NO.

11.
BUDGET ACTIVITY:

RESEARCH /_/ ADMINISTRATION /_/

REVIEW & APPROVAL /X/ TECHNICAL ASSISTANCE /X/

12. Cancer training centers throughout the country
COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 or 1957

13. None
IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

14, 15 and 16 - None

PROJECT REPORT FORM

1. National Cancer Institute — INSTITUTE
2. Field Investigations and Demonstrations Br. — LABORATORY OR BRANCH
3. Nursing — SECTION OR SERVICE
4. T-6 — LOCATION (IF OTHER THAN BETHESDA)
5. NCI 105 — SERIAL NO.

6. Cancer Nursing Institutes — PROJECT TITLE

7. Margaret Knapp, F. Ruth Kahl, Mary Bouser — PRINCIPAL INVESTIGATORS

OTHER INVESTIGATORS

PROJECT DESCRIPTION

(1) Objective

1) to improve and extend knowledge regarding cancer among nurses.
2) to stimulate further study in cancer
3) to help nurses become more alert to detect symptoms and signs of cancer among constituents served by them.

(2) Methods Employed

Responsibility for planning of institutes vested with local committee.
Preplanning visit made when possible and if not possible, assistance given through correspondence and by telephone.

Institutes were of one or two days duration.

Attendance ranged from fifty to three hundred and fifty.

Lectures, visual aids, role playing and group projects were methods used at most sessions.

Three days of preplanning meetings were conducted in Montana. Eight Institutes were conducted in South Carolina and one in Kentucky.

(3) Major Findings

Difficult to evaluate results. There is evidence of tremendous enthusiasm at the time of the meetings and by the planning committee in the post evaluation conference.

(4) Significance to Cancer Nursing Section

Institutes bring together nurses from universities, hospitals, industry and public health. We find nurses who are able to serve

as resource people for other educational activities in local communities. Occasionally we find universities and schools of nursing which are willing and able to test the reliability of the educational tools we are developing.

(5) Proposed Course of Project

To encourage planning group to conduct their own cancer nursing institutes if resource persons are available.

PROJECT REPORT FORM (Cont d)

NCI 105
SERIAL NO.

BUDGET ACTIVITY:

RESEARCH [ ] ADMINISTRATION [ ]

REVIEW & APPROVAL [ ] TECHNICAL ASSISTANCE [X]

12. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 or 1957

Cooperating Relationships

Within the Service:

Institutes were promoted by the Regional Nursing Consultants. Preplanning meetings and institutes were joint activities with Regional and Central Office Nursing Personnel.

Other:

Within the states the sponsors and cooperating units are the nurses from the State Department of Health - Universities, the State Professional Nursing Organizations and the State Sections of the American Cancer Societies.

13. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

Similar to other Control Programs for other disease categories.

No entries for items 14, 15, and 16.

PROJECT REPORT FORM

1. National Cancer Institute — INSTITUTE
2. Field Investigations and Demonstrations Br. — LABORATORY OR BRANCH
3. Nursing — SECTION OR SERVICE
4. T-6 — LOCATION (IF OTHER THAN BETHESDA)
5. NCI 106 — SERIAL NO.

Teacher Training Institute at University of Tennessee
PROJECT TITLE

Margaret F. Knapp
PRINCIPAL INVESTIGATOR(S)

Margaret Denham (Nursing Consultant - Heart Program)
OTHER INVESTIGATORS

PROJECT DESCRIPTION

(1) Objective

To help prepare nursing instructors from the University of Tennessee School of Nursing Faculty and representatives from the supervisory staff at John Gaston Hospital.

(2) Method

a. One week was spent exploring local facilities and services

b. The local faculty formed committees, defined problems, developed a program to meet their objectives. F.I.D.B. and cardiac nursing consultants gave guidance and consultation.

c. Institute held after 3 months of preplanning.

d. F.I.D.B. nursing consultant served as resource person at institute.

e. F.I.D.B. nursing consultant conducted post evaluation conference.

(3) Major Outcomes

1. Doctors and nurses became aware of problems inhibiting maximum learning situations for student nurses.

2. The need for continuity of nursing care for the discharged cancer patients needing treatment as in terminal illness led to the appointment of a committee to set up a referral system. Both the community agencies and the hospital personnel and faculty were members of the committee.

PROJECT REPORT FORM (Cont'd)

3. The faculty felt they were not ready to conduct teacher training institutes in other parts of the State until they had resolved some of their own problems.

(4) Significance

1. The work conference has led to better preparation of student nurses to meet problems of cancer patients.

2. Student nurses who have greater cancer knowledge will be better able to participate in cancer control programs leading to early case findi

(5) Proposed Course

1. To have a follow-up institute.

2. To implement the referral system.

3. To help plan for teacher training projects to be conducted in other parts of Tennessee.

PROJECT REPORT FORM (Cont'd)

12. NCI 106
SERIAL NO.

11.
BUDGET ACTIVITY:

RESEARCH	☐	ADMINISTRATION	☐
REVIEW & APPROVAL	☐	TECHNICAL ASSISTANCE	[X]

13.
COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 or 1957

1. This was a joint undertaking with the Nursing Section, Heart Disease Control Branch, Special Health Services, State Services.

2. Other cooperating units were: Local public health agencies, Cancer Society and University of Tennessee.

14.
IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

No entries for items 14, 15, and 16.

PROJECT REPORT FORM

1. National Cancer Institute — INSTITUTE
2. Field Investigations and Demonstrations Br. — LABORATORY OR BRANCH
3. Nursing — SECTION OR SERVICE
4. T-6 — LOCATION (IF OTHER THAN BETHESDA)
5. NCI 107 — SERIAL NO

6. Consultation Service to five Universities receiving special project grants from NCI. — PROJECT TITLE

7. Rosalie I. Peterson and Margaret F. Knapp — PRINCIPAL INVESTIGATOR(S)

8. Dr. Hon — OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objective:

A. To give assistance to the Cancer Nursing Project Directors at Skidmore College, New York; Boston University; Washington University, St.Louis; Vanderbilt University and University of California-Los Angeles in accomplishing (1) Integration of Cancer Nursing in the Basic Professional Nursing Curriculum
   (2) Teaching a broad concept of cancer which would include knowledge of cancer and its problems, prevention, early detection, treatment, nursing care in hospital and home, and rehabilitation.
   (3) Using the monograph, "Cancer Nursing in the Basic Professional Curriculum" as a guide
   (4) Exploring the use of problem-solving as a method of teaching

B. Assist in refining and improving the Knowledge Test to evaluate the learning of cancer by student nurses

Method:

A. Visits to the grantee schools and meeting with the total nursing faculty to:

   a. discuss problems encountered in the study

   b. share in the interpretations and aid in solving some of the problems

   c. learn from them methods of overcoming obstacles

   d. observe nurse-patient relationships in the hospitals and clinics

PROJECT REPORT FORM (Cont'd)

B. Conduct work conferences so that all of the project directors

a. may attack mutual problem

b. may develop tools of evaluation

Major Finding:

1. Cancer is a disease in which basic principles of nursing can be taught

2. Cancer is an excellent area in which nurses may learn to give skilled comprehensive nursing care to a patient and his family.

3. It is extremely difficult to change a curriculum pattern which involve a total faculty and may involve the philosophy of the institution.

4. There must be wholehearted faculty participation if total integration of a disease entity is to be accomplished.

5. It would be easier to integrate several subjects at one time rather than only one as more faculty would be involved in the process.

6. The study at Washington University, St. Louis, Mo. was discontinued at the conclusion of its third year due to the abolishment of the collegiate program.

Significance to F.I.D.B. - Nursing Section

If cancer can be integrated throughout the basic professional curriculum, nurses will have greater knowledge of cancer, which should reflect in earlier case finding and better support of the patient and his family.

Proposed Course of Project

1. Continue evaluation and support of the project through the remaining period of the pilot study.

2. Depending upon the pregress of the pilot study determine whether a request for an extension of the grant should be supported in order to achieve integration.

3. Depending upon the results of the pilot study, determine whether furth expansion of this method of teaching should be planned for and encouraged or whether a new approach is needed.

PROJECT REPORT FORM (Cont'd)

1. NCI 107
SERIAL NO.

1. BUDGET ACTIVITY:

RESEARCH [ ] ADMINISTRATION [ ]

REVIEW & APPROVAL [ ] TECHNICAL ASSISTANCE [X]

1. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 or 1957

The faculty at all five grantee schools

All five schools have the same objective but the methods of approach may be different.

3. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

No entries for items 14, 15, and 16.

PROJECT REPORT FORM

1. National Cancer Institute — INSTITUTE
2. Field Investitations and Demonstrations Br. — LABORATORY OR BRANCH
3. Nursing Section — SECTION OR SERVICE
4. T-6 — LOCATION (IF OTHER THAN BETHESDA)
5. NCI 108 — SERIAL NO.
6. Work Conference for the Cancer Nursing Project Directors from the Five (University Schools of Nursing Which Are Recipients of Cancer Special Grants. — PROJECT TITLE
7. Rosalie I. Peterson, Margaret F. Knapp — PRINCIPAL INVESTIGATORS
8. Dr. Louis Heil (Consultant) — OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

1) Objectives:

(1) To share problems involved in integrating cancer nursing throughout the basic professional nursing curriculum.

(2) To make further plans for the implementation of the objectives of the grant.

(3) To prepare material for a Panel on Evaluation tools to be presented at the Biennial Convention of the National League for Nursing.

2) Method:

Each project director was asked

(1) To review objectives of grant

(2) To give evidence showing degree of progress of integration

(3) To be prepared to discuss obstacles or stumbling blocks which inhibited his progress.

(4) To list ways in which the nursing section of F.I.D.B. could help minimize or meet problem.

3) Major Findings:

(1) It has been difficult to integrate cancer nursing throughout the total curriculum. In most instances it has been accomplished in certain areas, i.e., Medical and Surgical Nursing.

(2) As several of the grantee schools are securing grants to integrate

other subjects (mental health, rehabilitation) they are finding strength in number and in greater willingness of faculty to look objectively at the problem of integration.

(3) All project directors helped to prepare the material for the panel at the Biennial and Doris Diller was selected to present the material.

4) Significance to the Program of F.I.D.B. Nursing Section:

An understanding of the difficulties of changing patterns of teaching and of philosophy will aid us in planning future programs.

Our work conference has shown us

(1) The type of preplanning needed to prepare schools to carry out such a project.

(2) The necessity for a longer period of time to achieve the objectives of a study that involves total faculty.

5) Proposed Course:

Further work conferences to share experiences and methods which have proved to be helpful.

PROJECT REPORT FORM (Cont'd)

NCI 108
SERIAL NO.

BUDGET ACTIVITY:

RESEARCH ☐ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE [X]

COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 or '57

The faculty at Skidmore College, N.Y.; Boston University, Boston; Vanderbilt University, Nashville, Tennessee; University of California, Los Angeles, and Washington University, St. Louis.

All five schools have the same objective - to integrate cancer nursing throughout the total curriculum.

IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

No entries for items 14, 15, and 16.

PROJECT REPORT FORM

1. National Cancer Institute — INSTITUTE
2. Field Investigations & Demonstrations Br. — LABORATORY OR BRANCH
3. Nursing — SECTION OR SERVICE
4. T-6 — LOCATION (IF OTHER THAN BETHESDA)
5. NCI-109 — SERIAL NO.

6. Revision of the Cancer Nursing Manual — PROJECT TITLE

7. Margaret F. Knapp — PRINCIPAL INVESTIGATOR

8. Nursing Staff F.I.D.B., Cancer Control Branch, New York State Dept. of Health — OTHER INVESTIGATORS

PROJECT DESCRIPTION

(1) Objective

To revise the Cancer Nursing Manual in order to bring statistics up-to-date

(2) Method

a. Manual was revised by Margaret F. Knapp with the assistance of the nursing staff of F.I.D.B.

b. This material was reviewed by the professional staff of the N.Y.State Division of Cancer Control.

c. One visit was made to New York City by principle investigator and Miss Peterson to complete the arrangements for printing.

(3) Major Outcomes

a. Cancer Nursing Section, F.I.D.B. has 20,000 copies of new manual.

b. One-half of these have been distributed.

PROJECT REPORT FORM (Cont'd)

10. NCI 109
SERIAL NO.

11.
BUDGET ACTIVITY:

RESEARCH [ ] ADMINISTRATION [ ]

REVIEW & APPROVAL [ ] TECHNICAL ASSISTANCE [x]

12.
COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 or 1957
Cooperative Relationships

New York State Department of Cancer Control Professional Staff.

13.
IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

No entries for items 14, 15, and 16.

PROJECT REPORT FORM

1. National Cancer Institute — INSTITUTE
2. Field Investigations & Demonstrations Br. — LABORATORY OR BRANCH

3. Nursing — SECTION OR SERVICE
4. — LOCATION (IF OTHER THAN BETHESDA)
5. NCI-110 — SERIAL NO.

6. Technical Assistance to States — PROJECT TITLE
(Study of methods to secure improvement and extension of p.h.n. services to cancer patients within state and local health departments.)

7. F. R. Kahl — PRINCIPAL INVESTIGATOR(S)

8. — OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

A. OBJECTIVE

Objective to increase number of patients who are diagnosed while cancer is in an early stage, to secure continuity of nursing care, and to increase p.h. nursing care in quality as well as amount, sufficiently to assure maximum rehabilitation of the cancer patients.

B. METHODS EMPLOYED

The development of an effective nursing consultation service thru acceptance by each nursing consultant of her responsibilities for cancer control in relation to her other functions: Example: The Maternal and Child Health Consultant recognized breast and uterine cancer as well as the various types of cancer occurring in children, as of special concern to her in her consultation.

C. P. H. NURSING ACTIVITIES INVOLVING PATIENT CARE INCLUDED

a. referral of individuals with suspicious signs and symptoms and follow thru until a diagnosis was secured. Record form designed in order to identify this information

b. staff education planned locally in order to meet the particular needs of the involved p.h. nurses

c. nursing visits to cancer patients reported to the state health department with emphasis on demonstrations of nursing care as individually ordered with subsequent visits for counselling and support of patient and families with the objective of maximum rehabilitation of the particular patient.

PROJECT REPORT FORM (Con't)

NCI-110
SERIAL NO.

D. MAJOR FINDINGS

a. Evaluation of nursing activities scheduled for January 1956 with expectation that project may be continued for a second year.

E. SIGNIFICANCE OF PROJECT

The major value of research in cancer is in its application to patient care, and we believe that nursing care is an important factor. This project is showing results in a more constructive attitude toward cancer among the public health nurses and consequently in an increased interest in finding the patient who may have cancer in an early stage.

10. NCI-110
SERIAL NO.

11.
BUDGET ACTIVITY:

RESEARCH ☐ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☒

12.
COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 OR 1957:

The nursing staff of the State and Local Health Departments in Iowa and Oklahoma are cooperating in the study. Conditions in the two states are very dissimilar. In Iowa there is a State Nursing Consultant Staff of 7 serving in as many special programs as well as a staff of 6 Regional Supervising nurses and 60 local health department staff public health nurses. While there are 9 cancer clinics in the state and their diagnosed cancer patients are reported to the State Health Department, these patients have only rarely been referred to p.h. nursing service. On the other hand Oklahoma currently has a state nursing consultant staff of 2, one in Mental Health and one in chronic diseases. In addition there are 5 regional supervising nurses and 96 local official agency staff nurses. Oklahoma has only 3 cancer clinics but in addition to reporting of their diagnosed cancer patients there is a fair amount of referral of patients to and from the p.h. nursing services. In both states there was a felt need to improve and extend their cancer nursing services and a desire to participate in a study of methods to accomplish this objective. Neither project has been completed.

13.
IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

None

NO ENTRIES FOR ITEMS 14, 15 & 16.

PROJECT REPORT FORM

1. Cancer INSTITUTE | 2. Field Investigations & Demonstrations Branch LABORATORY OR BRANCH

3. Field Studies Sections SECTION OR SERVICE | 4. Memphis, Tennessee LOCATION (IF OTHER THAN BETHESDA) | 5. NCI-111(c) SERIAL NO.

Vaginal Cytology as a means of Cancer Case Finding - Memphis-Shelby County.
PROJECT TITLE

Richard Malmgren, M. D.
PRINCIPAL INVESTIGATOR(S)

S. J. Cutler
OTHER INVESTIGATORS

PROJECT DESCRIPTION

(A) Objective

The Memphis-Shelby County Cytology Project has as its aim the examination of a sufficient number of females over the age of 20 in the Memphis-Shelby County area to assure that approximately 30,000 are re-examined two times, that is, three examinations in all. Objectives include: 1) Evaluation of vaginal aspiration as an efficient screening method for cervical cancer; 2) To obtain information upon the natural history of carcinoma-in-situ bearing upon: a) the true incidence and prevalence, b) the duration of the lesion, c) the course of carcinoma-in-situ with particular reference to regression and progression; 3) To obtain data indicating what may be expected from future widespread application of this technique.

(B) Methods Employed

A morbidity survey for uterine cancer was conducted in the Memphis-Shelby County area in 1950 and 1951 to act as a base of reference for the study. In July 1952 the cooperative cytology project was begun, and patients were examined with the cooperation of private physicians, clinics, and the health department. All positive and suspicious cases are referred for biopsy, which it is felt is the only definitive means of diagnosis. Re-examinations are done at 12 to 18 month intervals.

(C) Major Findings.

Over 100,000 females over the age of 20 years have been examined in Memphis. Hand sort data from the first 80,000 of these revealed that biopsy is recommended in 1,452, and at the time of recording, biopsies were completed in 1,200. Six-hundred and twenty-seven(627) confirmed uterine cancers were

NCI-111(c)
SERIAL NO.

PROJECT REPORT FORM (Cont'd)

found, of which 221 were intraepithelial lesions, and 288 were invasive carcinomas. One-hundred and forty-four (144) cases of atypical metaplasia are being followed. Data to date indicate that approximately eight (8) cases of uterine cancer per thousand examined are detected by this method, with somewhat over 50 percent being the early localized intraepithelial lesions. The early lesions continued to be almost 90 percent unexpected.

Of 25,000 women examined a second time during a period of 12 to 18 months, 177 have been biopsied to date yielding 55 confirmed cases. Forty-seven(47) of these are intraepithelial carcinoma and eight (8) are invasive cancer, but the invasive cases are described as early. Recheck of the initial slides on the first screening reveals that the false negatives .14 percent were due to probable misreading of the first slide, while .16 percent could not have been detected by the first slide. Combining the two together, a maximum on all false negatives to date is .03 percent, that is, .25 for intraepitheli and .05 for invasive, which are described as early invasive. Detailed analys is now being undertaken with the cards being punched and sorted for more definitive data.

(D) Significance to Cancer Research

This project has indicated that the vaginal aspiration is an efficient method of detecting uterine cancer. It is believed that further refinement of the data now available will demonstrate the most effective techniques and methods which will enable the launching of a widespread and integrated attack upon this disease, with a consequent great reduction in mortality.

(E) Proposed Course of Project

The present status of the project will be continued until 30,000 women have been examined for a third time. Further epidemiological study is bearin upon incidence rates, prevalence rates, the natural history of carcinoma-in-situ, environmental factors concerned with possible etiological effects, and specific information as to age and race differences are to be continued.

(F) Patient Material:

The Unselected adult female population of the Memphis-Shelby County area The three major sources of examination specimens are: (1) private physicians (2) regular daily clinics held at a local hospital (3) annual temporary clini held in large industries, hotels, banks, schools, etc.

PROJECT REPORT FORM (Cont'd)

NCI-111 (c)
SERIAL NO.

BUDGET ACTIVITY:

RESEARCH	/_/	ADMINISTRATION	/_/
REVIEW & APPROVAL	/_/	TECHNICAL ASSISTANCE	/X/

COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 or 1957:

The University of Tennessee College of Medicine, Division of Obstetrics and Gynecology and the Institute of Pathology

Memphis-Shelby County Health Department

IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

A number of parallel investigations under NCI research grants and several parallel studies in other geographical locations being conducted cooperatively by University groups and the Field Investigations and Demonstrations Branch.

ENTRIES FOR ITEMS 14, 15 & 16.

PROJECT REPORT FORM

1. Cancer INSTITUTE
2. Field Investigations and Demonstrations Branch LABORATORY OR BRANCH
3. Field Studies Section SECTION OR SERVICE
4. Bethesda, Md. LOCATION (IF OTHER THAN BETHESDA)
5. NCI-112 SERIAL NO.

CLINICAL TRIALS UNIT
PROJECT TITLE

Andrew G. Peacock, Ph.D.
PRINCIPAL INVESTIGATOR(S)

Miss Highsmith
OTHER INVESTIGATOR(S)

PROJECT DESCRIPTION.

The development and evaluation of general cancer diagnostic tests exclusive of cytology, relating to biochemical and immunologic procedures.

(A) Objective.

To develop tests capable of aiding in the detection of cancers of all sites in early stages of development. The overall aim is to develop one or more cancer diagnostic tests, that will be simple, inexpensive, easily duplicated, and therefore, applicable to large population areas on a mass basis.

(B) Methods Employed.

Basic research is employed upon chemical and immunological principles underlying tests described in the past, and principles which aid in the development of new tests. During the past year, the principles upon which some general tests for diagnosis have been based, have been evaluated. Modifications of these principles have been attempted, and new procedures have been adopted which may aid in the formulation of new tests. Procedures developed are evaluated upon the serum from known cancer patients, and from normal people.

(C) Major Findings.

Penn Test: Additional data accumulated on the Penn Test have continued to show that the reaction, in our experimental laboratory, gives a very large (about 25%) Proportion of false positive results in the normal population. We have confirmed that our techniques are correct by exchanging serums with the originators. Brief experience with a new (drastically)

PROJECT REPORT FORM (Cont'd.)

CI-112
SERIAL NO.

(C) Major Findings (Cont'd.)

change procedure by the originators has indicated that their change increases the specificity, but most seriously lowers the sensitivity and cancer patients.

Serum Acid Phosphatase: Acid phosphatases from a variety of sources have been studied to learn whether substances other than tartrate would be of value in the diagnosis of prostate cancer. To date none have been discovered. We have also examined the effects of substrate and tartrate concentration on the differentiation of "normal" and "prostatic" acid phosphatase, and believe that the methods now in use can be made more specific. Whether or not these changes will result in any increased sensitivity remains to be seen.

Density Test (Quinn, Rappoport): Preliminary work only has been carried out.

White Cell Alkaline Phosphatase: With Dr. George Brecher we have devised a simple method for the estimation of alkaline phosphatase in white cells. The level of this enzyme is sometimes of value to the hematologist in differentiating between certain types of early leukemias and infections.

(D) Significance to Cancer Research.

The development of any test that would aid in the detection of cancer in an early stage of one or more sites would be of an estimable value to the clinician. With strong suggestive evidence at hand that the patient has a cancer, the present diagnostic procedures could be intensified in studying this patient, and there would be impetus for the development of further refined diagnostic procedures. It is evident that that the development of such tests would be of great practical value in combating the cancer problem.

(E) Proposed Course of Project.

Although we had hoped to finish our work with the Penn test, it seems advisable to continue study on this project. We plan to continue work on the density test, and on our modifications in the acid phosphatase assay. We also plan to investigate the levels of serum lactic dehydrogenase, recently shown to be rather specifically elevated in cancer seru

PROJECT REPORT FORM (Cont'd.)

NCI-112
SERIAL NO.

NCI-112
SERIAL NO.

BUDGET ACTIVITY:

RESEARCH	☐	ADMINISTRATION	☐
REVIEW & APPROVAL	☐	TECHNICAL ASSISTANCE	☒

COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 or 1957:

None.

IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

Separate evaluation of Penn Test and other Serological Tests.

NO ENTRIES FOR ITEMS 14, 15 & 16.

PROJECT REPORT FORM

1. Cancer — INSTITUTE
2. Field Investigations and Demonstrations Branch — LABORATORY OR BRANCH
3. Field Studies Sections — SECTION OR SERVICE
4. San Francisco, California — LOCATION (IF OTHER THAN BETHESDA)
5. NCI-113 — SERIAL NO.

6. Changes in blood as a method of diagnosis in cancer of human beings. — PROJECT TITLE

7. J. E. Dunn — PRINCIPAL INVESTIGATOR(S)

8. S. Greenhouse — OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

(A) Objective

1) To evaluate the specificity and sensitivity of a serum flocculation test (Penn Test) for use in mass population screening to detect presence of cancer of any site in individuals.

(B) Methods Employed

1) A selected group of approximately a dozen hospitals and laboratories across the country are participating in this field trial of the Penn Test.

2) A questionnaire suitable for biometric coding for use of the laboratories was prepared, tested, evaluated and revised. The accepted forms have been provided for all participating laboratories to use in reporting the results of their trial runs of the Test.

3) Tests are being run on selected classes of blood samples routinely submitted to the laboratories on both known cancer cases and persons believed not to have cancer. Tests are also being run on some groups of general hospital admissions.

(C) Major Findings

Collection of data will be completed in the near future. Preliminary tabulations of incomplete data indicate that the test in hands other than the originators lacks sensitivity for cancer patients. Some of the difficulty may still lie with technical aspects of the test. One group, for example, was unable to overcome low specificity of the test. The test procedure, however, as presently described is not sensitive enough for general use.

PROJECT REPORT FORM (Cont'd)

NCI-113
SERIAL NO.

(D) Significance to Cancer Research

1) If a test can be developed that will reliably indicate which persons have a cancer of some site, by use of general screening techniques the segment of the populace in need of cancer diagnosis and treatment can be identified.

2) Present cancer case finding methods require much diffusion of effort and funds on screening by modified but time consuming physical and x-ray examinations. Successful development of a simple blood test for case detection will permit concentration on cancer diagnosis and treatment in individuals.

(E) Proposed Course of Project

To complete the collection of clinical histories in test individuals and make a final analysis of results.

PROJECT REPORT FORM (Cont'd)

NCI-113
SERIAL NO.

BUDGET ACTIVITY:

RESEARCH	[ ]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	TECHNICAL ASSISTANCE	[X]

COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 or 1957:

Cooperating hospitals and laboratories selected by the California Study Group.

IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

None.

ENTRIES FOR ITEMS 14, 15 & 16.

PROJECT REPORT FORM

1. Cancer INSTITUTE
2. Field Investigations & Demonstrations Branch LABORATORY OR BRANCH
3. Field Studies Sections SECTION OR SERVICE
4. St. Louis, Missouri LOCATION (IF OTHER THAN BETHESDA)
5. NCI-114(c SERIAL N

6. Prevalence of Gastric Achlorhydria in Selected Population Groups: and Evaluation of Tubeless Gastric Analysis as a Screening Test for Gastric Cancer. PROJECT TITLE

7. Dr. M. Sievers PRINCIPAL INVESTIGATOR(S)

8. Dr. W. S. Baum OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

(A) Objectives.

1) Estimation of the prevalence of gastric achlorhydria in selected adult population groups using a newly developed technique of tubeless gastric analysis.

2) Determination of the usefulness and practicability of the new gastric analysis technique in multiphasic or single phasic health screening of population groups.

3) Evaluation of possible correlation between occurrence of gastric achlorhydria and of gastric cancer.

(B) Methods Employed

1) Evaluating gastric acidity in individual patients by both intubation and the tubeless gastric analysis to determine the accuracy of the tubeless method.

2) Performance of tubeless gastric analysis in mass population groups to determine incidence of achlorhydria.

3) Study of those patients with achlorhydria, including gastro-intestinal x-ray examination and prolonged followup to determine incidence of gastric cancer.

PROJECT REPORT FORM (Cont'd)

NCI-114(c)
SERIAL No.

(C) Major Findings

1) Confirmation of the high degree of accuracy of tubeless gastric analysis using a quinine resin as compared to intubation results, as has also been well established in 11 reports in the literature with a combined accuracy figure of over 98%. (1,280 controlled tests).

2) Establishment of the fact that a new azure A resin for the tubeless gastric analysis reproduces the results of the quinine resin in about 96% of 93 individuals tested.

(D) Significance to Cancer Research.

It has been known for many years that gastric cancer occurs much more frequently (about seven times) when achlorhydria is present. More accurate surveys of incidence of achlorhydria and the long-time follow-upof the individuals with achlorhydria is desirable to develop more detailed information on the relationship. The simplicity of the tubeless technique makes it especially desirable for this study. This project will also evaluate the usefulness of tubeless gastric analysis as a screening technique for identifying the individuals most apt to have or to develop gastric cancer. It will evaluate whether further definitive tests in this achlorhydric group is a useful combination-procedure for detecting gastric cancer.

(E) Proposed Course of Project

1) Clinical trials to perfect skill and reliability in performing the tubeless gastric analysis.

2) Investigation of the oral use of gastric secretory stimulants for confirmation of test findings.

3) Conduct screening tests on unselected consecutive hospital admissions and subject those with achlorhydria to definitive examinations and to long-time follow-up study concerning the development of gastric cancer.

4) Extend the screening tests to industrial population groups.

(F) Patient Material

Selected patients with gastric symptoms and without gastric symptoms who are seen on the medical and gastro-intestinal services of the PHS dispensary and of two hospitals in a midwestern city.

PROJECT REPORT FORM (Cont'd)

). NCI-114(c)
SERIAL NO.

1. BUDGET ACTIVITY:

RESEARCH	/_/	ADMINISTRATION	/_/
REVIEW & APPROVAL	/_/	TECHNICAL ASSISTANCE	/X/

2. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 or 1957:

Veterans Administration Facility, St. Louis, Missouri

3. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

None.

IO ENTRIES FOR ITEMS 14, 15 & 16.

PROJECT REPORT FORM

1. Cancer Institute	2.	Field Investigations & Demonstrations Branch LABORATORY OR BRANCH		
3. Field Studies Sections SECTION OR SERVICE	4.	St. Louis, Missouri LOCATION (IF OTHER THAN BETHESDA)	5.	NCI-115- SERIAL NO.

6. Survival, incidence and prognosis factors in a selected group of gastric cancer patients.
PROJECT TITLE

7. Dr. M. Sievers
PRINCIPAL INVESTIGATOR(S)

Dr. S. C. Ingraham, II
OTHER INVESTIGATORS

PROJECT DESCRIPTION

(A) Objectives

1) Evaluation of Factors common to 5-year survivors of gastric cancer which might bear on their survival.

2) Evaluation of factors in gastric cancer patients which occur more frequent than in the general population and may be related to the incidence of malignancy in the individuals.

3) Evaluation of the factors in gastric cancer patients which may be pertinent to the prognosis of this condition.

(B) Methods Employed

1) Review and abstract of clinical and hospital charts of all admissions to a large midwestern hospital for gastric malignancy during the past decade.

2) Compilation of relevant statistical factors for other, large population groups for comparison with this group, including data on blood groups from the blood bank.

3) Current follow-up on all patients of the group to determine their survivorship and ultimate fate through personal contacts with patients, or their relatives, through the hospital social service department and through visits to the hospital cancer clinic by the patient.

PROJECT REPORT FORM (Cont'd)

NCI-115
SERIAL NO.

4) Search of vital records of appropriate communities for death certificat on patients known to be or suspected of being deceased.

5) Collation and biometric analysis of all data collected on the study group.

(C) Major Findings.

1) None. This project was started during the third quarter of calendar year 1954 continued on a part-time basis through 1955 and insufficient data is yet available to permit of reliable statistical analysis.

(D) Significance to Cancer Research.

1) Little statistically tested information is available relative to factor bearing on incidence, prognosis, and survival among patients with the estab ed diagnosis of gastric cancer. This study offers promise of providing som of these data.

(E) Proposed Course of the Project.

1) The hospital charts and other sources of information on gastric cancer patients is to be examined looking for factors common to 5 year survivors such as similarities in blood type, or items related to age, sex, race, religion, marital status, etc.

2) Collected data will be subjected to statistical analysis and other scrutiny as may appear desirable in attaining the listed objectives of the project.

3) Pathological specimens of 5-year survivors will be reexamined carefully in an effort to determine factors important to survival.

PROJECT REPORT FORM (Cont'd)

NCI-115
SERIAL NO.

BUDGET ACTIVITY:

RESEARCH [ ] ADMINISTRATION [ ]

REVIEW & APPROVAL [ ] TECHNICAL ASSISTANCE [X]

COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 or 1957:

None.

IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

None.

ENTRIES FOR ITEMS 14, 15 & 16.

PROJECT REPORT FORM

1. Cancer — INSTITUTE
2. Field Investigations and Demonstrations Branch — LABORATORY OR BRANCH
3. Field Studies Section — SECTION OR SERVICE
4. Boston, Mass. — LOCATION (IF OTHER THAN BETHESDA)
5. NCI-116(C — SERIAL NO.

Clinical and Environmental Study of Mothers of Children With Malignancy Other Than Hematopoietic.
PROJECT TITLE

Dr. Miriam Manning
PRINCIPAL INVESTIGATOR(S)

S. C. Ingraham, II, M. D.
OTHER INVESTIGATORS

PROJECT DESCRIPTION

(A) Objective.

1) This study was listed in 1954 as NCI-116. Findings in 1955 have made it desirable to separate NCI-116 into a "leukemia project", a "lymphomata" project and an "other cancer" project. This is the "other cancer" project.

2) To determine whether the correlation of occurrence of leukemia in children with history of certain environmental exposures of their mothers carries over to other cancers of childhood.

3) To discover etiological factors in cancer of childhood other than leukemia.

4) To use as possible control group for project #1.

5) To determine whether malignancies of childhood, other than leukemia, differ among themselves in maternal environment, medical history, industrial or other exposure to possible carcinogenic agents.

(B) Methods Employed.

1) This study evolved from an investigation of possible environmental causes of leukemia in children. Experience during 1954 has made it desirable to expand the study to consider all types of cancer in children and to separate it into several discrete projects of which this is one.

NCI-116(C)
SERIAL NO.

PROJECT REPORT FORM (Cont'd.)

(B) Methods Employed (Cont'd.)

Medical and hospital records of children diagnosed in selected hospitals in New England as having cancer are reviewed.

3) Families of these cancer patients are interviewed with regard to maternal environmental exposures, and family and personal medical history. Particular attention is paid to history of radiation exposure and allergic disease.

4) Data for all patients and families in the study are collated in search for factors common to appreciable numbers of the cases.

(C) Major Findings.

This project has yielded statistically stable results showing that mothers of children having malignancies other than leukemia or lymphomata give definitely different histories of environmental exposure than do mothers of leukemic children. Results thus far tabulated indicate that a significantly lower number of mothers in this group have a history of hay fever, asthma or hives. At this time, this is the only noteworthy factor tabulated in this project.

(D) Significance to Cancer Research.

The maternal difference thus noted (lower occurrence of allergy) may well be one step in uncovering the etiology of malignancies in childhood. If different etiologies exist for the different forms of childhood cancer, the data from this project should help highlight these differences.

(E) Proposed Course of the Project.

1) To continue the present collection of data until statistically significant numbers are obtained.

2) Biometric analysis of data as it accumulates.

3) Possible extension of a similar inquiry to adults with malignancies.

PROJECT REPORT FORM (Cont'd.)

-116(C)
AL NO.

NCI-116(C)
SERIAL NO.

BUDGET ACTIVITY

RESEARCH	☐	ADMINISTRATION	☐
REVIEW & APPROVAL	☐	TECHNICAL ASSISTANCE	☒

COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 or 1957:

Children's Hospital, Boston, Mass.
Children's Cancer Research Foundation, Children's Medical Center, Boston, Mass.

IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

None.

NTRIES FOR ITEMS 14, 15 & 16.

PROJECT REPORT FORM

1. Cancer INSTITUTE
2. Field Investigations & Demonstrations Branch LABORATORY OR BRANCH
3. Field Studies Sections SECTION OR SERVICE
4. Boston, Massachusetts LOCATION (IF OTHER THAN BETHESDA)
5. NCI-117 SERIAL NO.

Leukemia Occurrence in the New England States
PROJECT TITLE

Dr. Miriam Manning
PRINCIPAL INVESTIGATOR(S)

Mr. Lawrence, B. E. Carroll
OTHER INVESTIGATORS

PROJECT DESCRIPTION

(A) Objective

To determine the occurrence of leukemia by town, and age group in the six New England States, thus giving an objective analysis of leukemia in a selected area.

(B) Methods Employed

1) Conference with State Health Officer in the Selected States to gain their interest and cooperation in the study.

2) Visiting the departments of vital statistics to get cases by age, residence and any other pertinent data that is available such as certificate informations.

3) Obtaining population data from states - by age, county, and town.

4) Calculation & collation of rates, by age, town and county.

5) Comparison of data for variance, from one locale to another.

PROJECT REPORT FORM (Cont'd)

NCI-117
SERIAL NO.

(C) Major Findings

There are statistically significant differences in case rates in some counties in Massachusetts, New Hampshire, Rhode Island and Vermont. These differences do not coincide with difference in population density. Other states have not yet been studied.

(D) Significance to Cancer Research

1) It will provide accurate data for leukemia occurrence in one geogra area.

2) Geographic areas are being located where detailed environmental studies should be done in connection with occurrence of leukemia.

3) This study may help elucidate some factors in the etiolgy of leuken

4) The leukemia data thus detailed is available for comparison with tha from other cancer in children and adults.

(E) Proposed Course of the Project

1) To complete collection of data on states already started.

2) To initiate data collection for selected states not yet studied.

3) To map, collate and correlate leukemia distribution and rates.

4) To subject to statistical analysis the results compiled.

5) To study in detail environmental factors in all areas where the occurrence of leukemia is high, in an effort to evaluate possible causative factors.

6) If meaningful results occur, to extend the study to other forms of cancer.

PROJECT REPORT FORM (Cont'd)

NCI-117
SERIAL NO.

BUDGET ACTIVITY:

RESEARCH	[ ]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	TECHNICAL ASSISTANCE	[X]

COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 or 1957:

Massachusetts State Health Department.
New Hampshire State Health Department.
Vermont State Health Department
Connecticut State Health Department.
Rhode Island State Health Department.

IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

None

ENTRIES FOR ITEMS 14 15 & 16.

PROJECT REPORT FORM

Cancer — 2. Field Investigations & Demonstrations Branch and Biometry and Epidemiology Branch
INSTITUTE — LABORATORY OR BRANCH

Field Studies Sections and Biometry Section — 4. — 5. NCI-118
SECTION OR SERVICE — LOCATION (IF OTHER THAN BETHESDA) — SERIAL NO.

Geographical Incidence of Cancer of Major Sites in Upstate New York
PROJECT TITLE

B. Carroll, Pope Lawrence
PRINCIPAL INVESTIGATOR(S)

S. C. Ingraham, II
OTHER INVESTIGATORS

PROJECT DESCRIPTION

(A) Objectives

1) To study the geographical pattern of cancer incidence for selected sites in Upstate New York.

2) To relate the findings to data from other studies of incidence and mortality.

(B) Methods Employed

1) The New York State Department of Health has made available its punch cards for reported cancer cases for the years 1949-1951. The data are believed to be unusually complete and accurate. These will be analyzed by county, city, and Statewide urban-rural groupings, using the indirect method of adjustment for age, sex, and urban-rural residence. A deck of 1950 New York Population cards was purchased from the Bureau of the Census to furnish the population bases for computing rates.

(C) Major Findings

1) Age specific incidence rates have been computed and age-adjustment carried out by mechanically computing expected numbers of cases for each of several cancer sites for the urban and rural portions of each county and for each urban place. Tests of significance are being carried out between expected and observed numbers for each site for each county, and for each city over 10,000 population.

PROJECT REPORT FORM (Cont'd)

NCI-118
SERIAL NO.

(D) Significance to Cancer Research

1) There is a need for systematic compilation of geographical variations in incidence and mortality in order to learn of any patterns which may emerge. Hypotheses as to cancerigenic factors often imply characteristic geographical distributions which can be verified or refuted by analyses of this kind.

(E) Proposed Course of Project

It is expected that analysis will be completed within the next few months. The type and nature of follow-up studies, if any, will depend on the findings

PROJECT REPORT FORM (Cont'd)

NCI-118
SERIAL NO.

BUDGET ACTIVITY:

RESEARCH	☐	ADMINISTRATION	☐
REVIEW & APPROVAL	☐	TECHNICAL ASSISTANCE	☒

COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 or 1957:

New York State Department of Health.

IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

None.

NTRIES FOR ITEMS 14, 15 & 16.

PROJECT REPORT FORM

Cancer INSTITUTE | 2. FIELD INVESTIGATIONS & DEMONSTRATIONS BRANCH LABORATORY OR BRANCH

Field Studies Sections SECTION OR SERVICE | 4. Boston, Mass. LOCATION (IF OTHER THAN BETHESDA) | 5. NCI-119 SERIAL NO.

Cancer Mortality in several selected population groups in New England
PROJECT TITLE

R. Taylor, B. Carroll
PRINCIPAL INVESTIGATOR(S)

S. C. Ingraham, II
OTHER INVESTIGATORS,

PROJECT DESCRIPTION

(A) Objectives

1) Evaluation of cancer occurrence rates in selected population groups living carefully supervised and regulated lives.

2) Comparison of cancer rates in the study population with those in the general population.

(B) Methods Employed

1) Names and identifying data are obtained on members comprising the study group (aggregating approximately 6000 persons) and pertinent data on environment, personal medical history, etc., are tabulated.

2) Vital records of the appropriate communities are searched for death certificates on deceased members of the group. The study includes individuals dying as early as 1875 and as late as 1954.

3) Appropriate tabulation, collation and biometric analysis is made of the data to discover similarities to and differences from similar data relative to the general population as corrected for age and sex distribution of the study group.

(C) Major Findings

None. This study is expected to be completed and an appropriate report prepared by the end of fiscal year 1956.

PROJECT REPORT FORM (Cont'd)

ICI-119
SERIAL NO.

(D) Significance to Cancer Research

Considerable information is available covering cancer occurrence in the general population and many occupation groups. Little is known about cancer in the supervised and regulated population groups, certain of which are typified by this study group. The comparison made possible by this study may well help uncover items in cancer etiology previously obscured by the relative homogeneity of the general population.

(E) Proposed Course of the Project

1) All data on population and deaths have been collected.

2) Progress has been held up due to press of other projects and shortage of clerical help. It is expected that work will be resumed and the project completed witin the next few months.

PROJECT REPORT FORM (Cont'd)

NCI-119
SERIAL NO.

BUDGET ACTIVITY:

RESEARCH	☐	ADMINISTRATION	☐
REVIEW & APPROVAL	☐	TECHNICAL ASSISTANCE	☒

COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 or 1957:

None.

IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

None.

ENTRIES FOR ITEMS 14, 15 & 16.

PROJECT REPORT FORM

1. Cancer	2.	Field Investigations & Demonstrations Branch & Biometry & Epidemiology Branch	
INSTITUTE		LABORATORY OR BRANCH	
Field Studies Sections &/	4.	Biometry Section Bethesda, Md. & Chicago, Ill.	5. NCI-120
SECTION OR SERVICE		LOCATION(IF OTHER THAN BETHESDA)	SERIAL NO.

Cancer as a cause of death and disability in railroad workers
PROJECT TITLE

S. Ingraham, B. Carroll
PRINCIPAL INVESTIGATOR(S)

P. Lawrence, F. Young
OTHER INVESTIGATORS

PROJECT DESCRIPTION

(A) Objectives

1) To determine occupational and other group differentials in mortality and disability from cancer of various sites (with particular attention to the lung) among employees in the railroad industry.

2) To make comparisons with figures for the general population. Any similarities or differences found can serve as leads for detailed investigations as to specific etiological factors (possibly in cooperation with railroad medical departments.)

(B) Methods Employed

1) A cohort of all railroad employees with at least 10 years of service, either active in 1951 or retired by the end of 1951, has been set up, numbering about 1,000,000 persons. Data for this cohort covering mortality from all causes and disability retirements due to cancer have been or will be assembled at RRB headquarters from punch-card files and from claims. The desired data are being supplied to the Institute in the form of duplicate punch cards, tabulations, and claim data representing the defined cohort and the deaths and disabilities occurring among members of the cohort each year. It is expected this cohort will be followed for 3 to 5 years at least. Data will be available to classify members of the cohort and the cancer cases as to age, sex, length of service, occupation, and employer for making both gross and detailed comparisons. Since all causes of death are being accounted for, data

NCI-120
SERIAL NO.

PROJECT REPORT FORM (Cont'd)

will be available of possible interest to other Institutes. The Heart Institute paid part of the cost of the project for the first year's data.

(C) Findings

None as yet.

(D) Significance to Cancer Research

1) Railroad employees constitute an occupationally stable group with their own retirement system. This is an ideal setting in which to attempt investigation of occupational factors and will provide good experience for later handling occupational data collected in Social Security Board operations. Certain railroad employees are known to be exposed to carcinogenic agents, and we have here a direct means of observing the effects. With a defined cohort, holding certain occupational factors constant, it should be possible to supplement the RRB records with collection of additional details on personal histories (in cooperation with individual railroads) to test association with other factors.

(E) Proposed Course of the Project

During the first 2 years the operational details of collecting the data from RRB files has been worked out, the cards for the cohort have been selected and tabulated, and 1 year's mortality and disability data have been compiled on data sheets. The coding of data sheets has almost been completed in preparation for card punching. It is expected that within a few months tabulations will be completed for the first year's results(1952) Work is going forward in Chicago on the copying of mortality and disability data occurring in 1953. These data sheets should be delivered to NCI in the near future.

PROJECT REPORT FORM (Cont'd)

NCI-120
SERIAL NO.

BUDGET ACTIVITY:

RESEARCH	/_/	ADMINISTRATION	/_/
REVIEW & APPROVAL	/_/	TECHNICAL ASSISTANCE	/X/

COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 or 1957:

National Office of Vital Statistics
Railroad Retirement Board

IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

None.

ENTRIES FOR ITEMS 14, 15 & 16.

PROJECT REPORT FORM

1. Cancer — INSTITUTE
2. Field Investigations & Demonstrations Branch — LABORATORY OR BRANCH
3. Field Studies Sections — SECTION OR SERVICE
4. Atlanta, Georgia — LOCATION (IF OTHER THAN BETHESDA)
5. NCI-121(C — SERIAL NO

Oral Cancer in Relation to Vitamin Deficiency and/or Use of Snuff
PROJECT TITLE

William R. Vogler, M.D.
PRINCIPAL INVESTIGATOR(S)

Samuel C. Ingraham, II, M.D.
OTHER INVESTIGATORS

PROJECT DESCRIPTION (Project reactivated approximately 11/28/55.)

(A) Objective

To seek possible relationships between occurrence of oral or pharyngeal cancer and vitamin deficiencies and/or the use of snuff (pulverized tobacco).

(B) Methods Employed

1) Review of pertinent hospital records in selected hospitals at Atlanta, Georgia for cases of diagnosed cancer of the oropharyngeal area.

2) Abstract and collation of appropriate data, from records of the cancer cases and interview of the patients, in search for factors common to groups of the study population.

(C) Major Findings

1) Approximately 15% of patients with cancer of the oropharynx had avitaminosis.

2) 70% of women with cancer of the buccal mucosa had been snuff dippers.

3) 40% of patients with cancer of the tongue were women (apparently there was no relationship in this group to use of snuff).

4) The ratio of women with cancer of the buccal mucosa to men with cancer of the same area is 1:1.

NCI-121(C)
SERIAL NO.

PROJECT REPORT FORM (Cont'd)

(D) Significance to Cancer Research

This investigation, as far as it proceeded, hints at a specific relationship between use of snuff and/or avitaminosis and the occurrence of cancer of the upper gastrointestinal tract.

(E) Proposed Course of the Project

Approximately the end of November 1955, Assistant Surgeon (R), William Vogler was transferred to Emory University Medical School and assigned to continue this project. The records and previous biometric analysis of data gathered have been turned over to Dr. Vogler. He is preparing his protocal for the continuation of this study.

(F) Patient Material

The records of selected hospitals in Atlanta, Georgia are searched for cases of cancer of the oropharyngeal area. Many of these patients are interviewed.

PROJECT REPORT FORM (Cont'd)

NCI-121(C)
SERIAL NO.

BUDGET ACTIVITY:

RESEARCH	/_/	ADMINISTRATION	/_/
REVIEW & APPROVAL	/_/	TECHNICAL ASSISTANCE	/X/

COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 or 1957

None.

IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

None.

ENTRIES FOR ITEMS 14, 15 & 16.

PROJECT REPORT FORM

1. Cancer — INSTITUTE
2. Field Investigations & Demonstrations Branch — LABORATORY OR BRANCH
3. Field Studies Sections — SECTION OR SERVICE
4. Boston, Massachusetts — LOCATION (IF OTHER THAN BETHESDA)
5. NCI-122(C) — SERIAL NO.

6. Industrial exposures, lymphoma and leukemia — PROJECT TITLE

7. Dr. John Vander, Dr. Miriam Manning — PRINCIPAL INVESTIGATOR(S)

8. Pope A. Lawrence, Henry Greenville — OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

(A) Objectives

1) To establish whether industrial exposure to possible carcinogenic agents can be correlated with the occurrence of leukemia or lymphoma in adults.

2) To determine whether the occurrence of leukemia or lymphoma in adults is a function of the amount and duration of exposure to possible carcinogenic agents.

3) To try to discover other environmental or familial factors which may lead to the development of leukemia or lymphoma in adults.

(B) Method Employed

1) Development of a question sheet to cover the information desired as to type and length of exposure. Question sheet also to contain pertinent points in patient medical history.

2) Personal interview with each patient to get desired information.

3) Where practical, visit to place or places of employment to evaluate what industrial exposure has occurred and to obtain guidance in this evaluation from employees and personnel of industry when practicable.

(C) Major Findings

This project was started late in 1955. There are no major findings at present.

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SERIAL NO.

PROJECT REPORT FORM (Cont'd)

(D) Significance to Cancer Research

1) This will add to the information on leukemogenic agents in industry.

2) It will correlate duration and amount of exposure with clinical history of patient.

3) It is expected to help orient employers and employees to potential existence of industrial health hazards.

4) It may identify materials not previously suspected as carcinogenic.

5) It may throw light on the etiology of leukemia in adults.

6) Control group for other cancer in adults.

(E) Proposed Course of Project

1) To take individual histories on all adults with leukemia in any form in a selected group of hospitals.

2) To analyze data as it accumulates to determine what changes should be made to make the study more effective.

3) To correlate data with similar data on other malignancies in adults

4) To obtain histories and determine occurrence rates for leukemia and other cancer in relation to degree of industrialization of selected geographic areas.

(F) Patient Material

Cases of leukemia or lymphoma which come to the attention of the State Industrial Commission, the State Health Service, and cooperating plant and private physicians.

PROJECT REPORT FORM (Cont'd)

NCI-122(C)
SERIAL NO.

BUDGET ACTIVITY:

RESEARCH	/_/	ADMINISTRATION	/_/
REVIEW & APPROVAL	/_/	TECHNICAL ASSISTANCE	/X/

COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 or 1957

None.

IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

None.

ENTRIES FOR ITEMS 14, 15 & 16.

PROJECT REPORT FORM

Cancer INSTITUTE | 2. Field Investigations & Demonstrations Branch LABORATORY OR BRANCH

Field Studies Sections SECTION OR SERVICE | 4. Salt Lake City, Utah LOCATION(IF OTHER THAN BETHESDA) | 5. NCI-123(C) SERIAL NO.

Study of Occupational Backgrounds of Hospitalized Cases of Lung and Bowel Cancer, Leukemias, and Primary Malignant Tumors of Bone, in Males over the Age of 25
PROJECT TITLE

J. W. Egan, M.D.
PRINCIPAL INVESTIGATOR(S)

S. C. Ingraham, II, M.D., B. E. Carroll
OTHER INVESTIGATORS

PROJECT DESCRIPTION

(A) Objective

1) To determine what occupational backgrounds are found in cases of the above-mentioned malignancies in order to focus attention on any occupations which by reason of frequent listing might be suspected of predisposing to the specific malignancy.

2) To gather data on possible environmental carcinogens.

(B) Methods Employed

1) Major hospitals in Utah and Western Colorado are cooperating in this project by having members of the house staff obtain detailed occupational and environmental exposure histories on specially prepared forms on all cases of lung and bowel cancer, leukemias, and malignant tumors of bone.

2) Data on all the cases will be examined, collated and otherwise analyzed biostatistically in search of factors common to the personal and working histories of the patients.

(C) Major Findings.

The first histories were obtained in January 1955, and too few cases have been submitted to date (through November 1955) to make analysis practicable. Histories have been submitted on 24 cases of lung cancer, 10 cases of large bowel cancer, 15 cases of leukemia, and no cases of malignant bone tumors.

NCI-123(C)
SERIAL NO.

PROJECT REPORT FORM (Cont'd)

(D) Significance to Cancer Research

It is hoped that this study may make available information on environmental factors in the causation of cancer.

(E) Proposed Course of the Project

1) Continued accrual of cases until statistically meaningful numbers have been collected.

2) Biostatistical analysis for appearance of correlatable items of information.

(F) Patient Material

All cases of lung and bowel cancer, leukemias, and malignant bone tumors in males seen in the major hospitals in Utah and Western Colorado.

PROJECT REPORT FORM (Cont'd)

0. NCI-123(C)
SERIAL NO.

1.

BUDGET ACTIVITY:

RESEARCH	/_/	ADMINISTRATION	/_/
REVIEW & APPROVAL	/_/	TECHNICAL ASSISTANCE	/X/

2

COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 or 1957:

Hospitals in Utah and Western Colorado.

IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

None.

ENTRIES FOR ITEMS 14, 15 & 16.

PROJECT REPORT FORM

1. Cancer INSTITUTE
2. Field Investigations & Demonstrations Branch LABORATORY OR BRANCH & Division of Special Health Services
3. Occupational Health Program
Field Studies Sections & / SECTION OR SERVICE
4. Salt Lake City, Utah LOCATION (IF OTHER THAN BETHESDA)
5. NCI-124(C) SERIAL NO.

Cancer Occurrence in Uranium Miners of the Colorado Plateau
PROJECT TITLE

James W. Egan
PRINCIPAL INVESTIGATOR(S)

P. A. Lawrence, Marian Erjavec
OTHER INVESTIGATORS

PROJECT DESCRIPTION

(A) Objectives

1) To determine the present state of health of as large a group as possible of underground uranium miners. (Approximately 1,100 miners comprise this base-group examined in the Summer of 1954).

2) To maintain contact with this basic group of men for an indefinite number of years in the future (possibly 15 or more years) in order to determine if there is an undue incidence of lung or bone cancer, leukemia or any other significant pathology among them.

(B) Methods Employed

1) Obtaining of detailed identifying data on the miners to facilitate contact with them for many years. This is obtained together with lifetime occupational and medical histories at the time that general physical examinations are performed. Included in the examinations are chest x-rays, and routine blood and urine examinations.

2) The men are contacted at least on an annual basis. This contact is either at the time of follow-up examinations or during an annual census of the industry.

3) Every effort is made to locate those who are found missing on the annual check. Devices outlined for locating those missing are as follows:

a) Letters to last known address.
b) Letters to last employer.

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SERIAL NO.

PROJECT REPORT FORM (Cont'd)

(B) Methods Employed (Cont'd)

c) Letters to relatives or friends

d) Check of death certificates, hospitals and physicians

e) Check on change of address as listed with the State motor vehicle or income tax bureaus

f) Check with local postmasters and church groups

g) Check with welfare agencies.

h) Check with Veterans Administration or BOASI as necessary

4) Newspapers from the Colorado Plateau are screened throughout the year for information concerning any uranium miners

5) The assistance of the Indian Health Service of the Public Health Service has been secured in maintaining contact with the Indian miners.

(C) Major Findings

1) In the Summer of 1954, 1,370 men were examined. Of these, 1,124 were underground miners on whom adequate baseline data were obtained. The remainder were mainly open pit or surface workers.

2) The abnormal medical findings have been totaled. It is not possible to state at this time that there have been any findings which could be related to radiation exposure. The data, however, must be coded and when that has been accomplished a more detailed analysis of the data may reveal some findings.

3) Between the summer of 1954 and 1955, eight deaths are known to have occurred in the group examined. Five deaths were traumatic, one was due to coronary thrombosis, one was due to primary carcinoma of the breast (which existed prior to the time the man began uranium mining), and one miner was burned to death.

4) In the Summer of 1955, a census of the entire uranium mining industry was made and a grand total of 2,202 men were contacted who probably represent 95% or more of the miners in the area. This figure includes names of miners from Wyoming and around Idaho Springs, Colorado, which were submitted in November, 1955. Of the 1,370 men examined in 1954, 668 were located in this census. On November 1, 1955, letters and questionnaires were sent out to the miners who had been examined in 1954 but who were not located by the census. This device as of November 30, 1955, resulted in the location of 327 additional men. Thus, as of this date, 995 of the 1,370 men have been located.

PROJECT REPORT FORM (Cont'd)

(D) Significance to Cancer Research

During the latter part of the last century and early part of this century, death rates from lung cancer in uranium miners in Europe were in the range of 50-75%. There is reason to believe, because of high concentrations of radioactive gas and dust in mines in this country, that a similar hazard could exist. It is believed desirable to evaluate the possible existence of similar risks for uranium miners in America.

(E) Proposed Course of Project

At least annual contact with the uranium miners previously examined will be maintained as outlined above. Morbidity and mortality statistics will be maintained. The optimum interval for repeat physical examinations has not yet been determined; but might be every 2 - 3 years.

(F) Patient Material

Efforts are made to include all uranium miners in the Colorado Plateau in this study.

PROJECT REPORT FORM (Cont'd)

10. NCI-124(C)
SERIAL NO.

11.
BUDGET ACTIVITY:

RESEARCH	[ ]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	TECHNICAL ASSISTANCE	[X]

12.
COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 or 195

Occupational Health Program of the Division of Special Health Services, Bureau of State Services, Public Health Service; Division of Biology and Medicine, Atomic Energy Commission.

13.
IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

None.

NO ENTRIES FOR ITEMS 14, 15 & 16.

PROJECT REPORT FORM

Cancer	2. Field Investigations & Demonstrations Branch, &	
INSTITUTE	LABORATORY OR BRANCH Office of Biometry	
Field Studies Sections	4.	5. NCI-125
SECTION OR SERVICE	LOCATION (IF OTHER THAN BETHESDA)	SERIAL NO.

The Incidence of Respiratory Cancer and Other Major Diseases Among World War I Veterans in Relation to Their Smoking Habits.
PROJECT TITLE

H. F. Dorn, W. S. Baum
PRINCIPAL INVESTIGATOR(S)

Raymond F. Kaiser
OTHER INVESTIGATORS

PROJECT DESCRIPTION

(A) Objective

To determine by direct observation of a defined cohort the mortality from respiratory cancer and other major diseases among male smokers and non-smokers in the age group of 50 and above.

(B) Methods Employed

Detailed smoking questionnaires were distributed by the Veterans Administration to approximately 300,000 World War I veterans who held active insurance policies. The study has now been in progress for two years. Detailed data from the smoking habits have been coded at the National Institutes of Health, and is being correlated with causes of death as listed on death certificate. In addition, at this time considerable effort is being expanded on writing to physicians, hospitals, and others concerned to obtain more precise information to supplement the mortality data from the death certificate. This data is then coded on the history card for ultimate analysis with the smoking history.

(C) Major Findings

It is estimated that at present, over 200 lung cancer deaths have occurred, in over 6,000 from all causes. Over 200,000 of the questionnaires were returned, and this group forms the basis for the present study.

NCI-125
SERIAL NO

PROJECT REPORT FORM (Cont'd)

(D) Significance to Cancer Research

The majority of data on smoking and its relation to respiratory cancer has been obtained from retrospective study, which show a wide range of magnitude for risk involved. If there is a risk, it is important to define rather precisely the degree of risk involved. Further, two other forward-looking studies on population groups are currently being conducted, and the present study will supplement data to be obtained from these studies.

(E) Proposed Course of Project.

The project will continue in its present form until coding is completed. No preliminary reports will be made since it is felt that no useful end would be served by such findings. It is planned to withhold the analysis until significant results may be obtained, which time is estimated to be approximately one year from now.

PROJECT REPORT FORM (Cont'd)

NCI-125
SERIAL NO.

BUDGET ACTIVITY:

RESEARCH	/_/	ADMINISTRATION	/_/
REVIEW & APPROVAL	/_/	TECHNICAL ASSISTANCE	/X/

COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 or 1957

Veterans Administration

IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

None.

ENTRIES FOR ITEMS 14, 15 & 16.

PROJECT REPORT FORM

1. Cancer INSTITUTE	2.	Field Investigations & Demonstrations Branch, & LABORATORY OR BRANCH		Office of Biometry
3. Field Studies Sections SECTION OR SERVICE	4.	Durham, N.C., Reidsville, Va. &/ Richmond, Va. LOCATION(IF OTHER THAN BETHESDA)	5.	NCI-126 (C) SERIAL NO.

The Occurrence of Cancer and Other Major Diseases Among Personnel Employed in The Manufacture of Cigarettes.
PROJECT TITLE

H. Dorn and W. S. Baum
PRINCIPAL INVESTIGATOR(S)

OTHER INVESTIGATORS

PROJECT DESCRIPTION

(A) Objective

The objective of this study was to determine the frequency of occurrence of cancer of the respiratory tract and of other major sites, and the frequency of occurrence of other major diseases among personnel engaged in the manufacture of cigarettes.

(B) Methods Employed

Through the cooperation of the American Tobacco Company a study was made of personnel and insurance records on employees over the period 1946 to 1952. Each employee who had served for a period longer than one year was covered by insurance with death benefits.

(C) Patient Material

Population at risk consisted of 12,000 cigarette workers under employ, for a period of 6 1/4 years. The number of person years of experience numbered 70,532.

(D) Major Findings

The study has been completed, and has been published in the J. of Indust. Med. & Surg. for June 1955. Results show that the expected number of deaths from respiratory cancer to be essentially the same as the observed numbers. The expected number of deaths from cancer of all forms is 36 percent greater than the observed, while the expected number of deaths from all diseases

NCI-126 (c) PROJECT REPORT FORM(Cont'd)
SERIAL NO.

(D) Major Findings(Cont'd)

combined is 48 percent greater than the observed. These data show that the mortality rate among these employees compares favorably with that of the general population of Virginia and North Carolina. In addition, cardiovascular diseases are reported less frequently as a cause of death for these employees than for the general population of North Carolina and Virginia. This Company provides an excellent medical care program for its personnel, and in addition, this study suggests methods which should be further pursued in other environmental fields.

(E) Significance of this Project

Literature in the past suggested a greater risk for respiratory cancer among personnel engaged in the handling of tobacco. This study did not support that point of view. It might further be reasoned that nicotine and other tobacco alkaloid effects were particularly marked in this group concerned with the handling and manufacturing of tobacco products.

(F) Proposed Course

None, project has been completed.

PROJECT REPORT FORM (Cont'd)

NCI-126(C)
SERIAL NO.

BUDGET ACTIVITY:

RESEARCH	/_/	ADMINISTRATION	/_/
REVIEW & APPROVAL	/_/	TECHNICAL ASSISTANCE	/X/

COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 or 1957

None.

IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

None.

PROJECT REPORT FORM (Cont'd)

14. NCI-126(C)
SERIAL NO.

15. PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 19

"Mortality among Workers in Cigarette Factories"
Industrial Medicine & Surgery 24: 239-241 June 1955

16. HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEA
1955:

None.

PROJECT REPORT FORM

Cancer 2. Field Investigations & Demonstrations Branch
INSTITUTE LABORATORY OR BRANCH

Field Studies Sections 4. 5. NCI-127
SECTION OR SERVICE LOCATION (IF OTHER THAN BETHESDA) SERIAL NO.

Frequency of Occurrence of Lung Cancer Among Selected Occupational Groups of Civil Service Personnel.
PROJECT TITLE

J. E. Carroll
PRINCIPAL INVESTIGATOR (S)

Because of lack of statistical-clerical time, this project is being held in abeyance for completion at a later date. It is considered well worth pursuing further. Also, however, it probably will not suffer by inactivation for a time as would other projects that have active cooperation and interest of persons outside the Public Health Service.

J.B. Hon, S. C. Ingraham
OTHER INVESTIGATORS

PROJECT DESCRIPTION

A) Objective

To determine the frequency of occurrence of respiratory cancer among selected groups of civil service personnel. With this data on hand, leads for further investigation of the occurrence of environmental cancers would be followed-up.

B) Methods Employed

The Civil Service Commission, because of retirement benefits, maintains complete files of medical diagnoses on personnel employed by this Commission. All cases of respiratory cancer listed, who had expired from this disease, were studied to obtain information on identifying number, address, sex, age, date of death, diagnosis, confirmation of diagnosis, place of death, length of service, and a complete occupational history. This information had already been tabulated for insurance purposes, and by bringing it together, valuable leads for environmental cancer studies might be obtained. Consequently, abstracts were made on 231 records of patients who had expired from respiratory cancer, and abstracts were made on 55 disability cases who had been treated for cancer of the respiratory tract. The majority of these deaths had occurred within the past three to four years.

(C) Major Findings.

Preliminary results indicate that on the majority of the cases there is a high percentage of microscopic confirmation of the diagnosis. Also, while a portion of the cases dates back for a period of 40 years, in many the occupational history commenced around 1940. Because of this it was felt that after

NCI-127
SERIAL NO.

PROJECT REPORT FORM (Cont'd)

analysis, more occupational history should be obtained if possible with the cooperation of the Civil Service Commission.

(D) Significance to Cancer Research

Incidence rates on the occurrence of respiratory cancer among selected occupational groups are virtually nonexistant. This study, if the mechanism for the obtaining of incidence rates could be set up in a department where the information is collected for other reasons, would provide an excellent source of information to further the studies now being undertaken in the etiologies o environmental cancer.

(E) Proposed Course of the Project.

It is planned to complete the analysis, and on the data obtained to date t the frequency of occurrence of respiratory cancer among the occupational group listed. Following this, further conferences will be held with the Civil Servi Commission in regard to the following two points. 1. The obtaining of additi- al occupational history on those patients who have expired. 2. The maintaini of a current file, so that this information may be collected from year to year

It is important to remember that in these records no individuals are identifie the records are identified by number only, and except for general results the study is a confidential one in which no information about any designated perso would be available to any person outside of the study group.

PROJECT REPORT FORM (Cont'd)

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SERIAL NO.

BUDGET ACTIVITY:

RESEARCH	/_/	ADMINISTRATION	/_/
REVIEW & APPROVAL	/_/	TECHNICAL ASSISTANCE	/X/

COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 or 1957:

None.

IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

This project resembles the study in Providence on data obtained from the State Unemployment Commission by Dr. John Vander. This study, however, is entirely retrospective, while Dr. Vander's study is forward-looking, since complete occupational histories will be taken from patients who have developed lung cancer. The two studies, however, might complement each other in obtaining leads for further investigation of potential environmental causes of cancer.

ENTRIES FOR ITEMS 14, 15 & 16.

Please read carefully (see ☞)

Name _____

Address _____

Please Complete:

Residence ☐ Undergraduate ☐

Graduate Student ☐ Professional Student ☐

Please check "Residence" or "Undergraduate" if this request is being made on your behalf by a parent, guardian, or other person. Please check "Graduate Student" or "Professional Student" if you are requesting your own records.

Please read carefully. Failure to do so may result in delay in processing your request.

Please check the appropriate box(es) below. If you are requesting your own records, please sign your name in the space provided. If you are requesting records on behalf of another person, please have that person sign his or her name in the space provided.

Please read carefully. Failure to do so may result in delay in processing your request.

PROJECT REPORT FORM

Cancer | 2. | Field Investigations & Demonstrations Branch
INSTITUTE

Cleveland, Ohio and Washington, D.C. | 5. | NCI-128
Field Studies Sections | 4.
SECTION OR SERVICE | LOCATION (IF OTHER THAN BETHESDA) | SERIAL NO.

Cancer among Railroad Workers in Certain Occupations.
PROJECT TITLE

P. Lawrence, B. Carroll
PRINCIPAL INVESTIGATOR(S)

Dr. S. Ingraham, F. Young
OTHER INVESTIGATORS

PROJECT DESCRIPTION

(A) Objectives

1) To study age and occupational patterns of cancer mortality among a particular segment of railroad employees.

2) To test the feasibility of obtaining the necessary data from the files of two brotherhoods with a view to securing more detailed information concerning cancer deaths.

3) To obtain and analyze detailed information on such items as method of diagnosis, histologic type, etc. for each case of death due to cancer among the membership.

(B) Methods Employed

1) Data have been obtained from the Insurance Department records of the Brotherhood of Railway Trainmen and the Brotherhood of Locomotive Firemen and Enginemen covering age, length of membership, and local lodge affiliation of all members carrying life insurance, and corresponding data for all insured members dying from 1950 through 1953. These cases are being looked up in death certificate files of NOVS to determine causes of death for analysis according to the variables indicated. Since this procedure has proved to be feasible, proposals have been made to the Brotherhoods and agreed upon for additional reporting and record provisions on the part of the brotherhoods. Under this agreement, beginning with the deaths occurring in January 1956, data on deaths will be furnished to us by the

NCI-128
SERIAL NO.

PROJECT REPORT FORM (Cont'd)

Brotherhoods and for each cancer death a letter and return report for will be sent by the Brotherhood to the attending physician requesting detailed information concerning the method of diagnosis, histologic be etc.

(C) Findings

1) None as yet. Cards have been punched from the data and sorted into the proper order. Several months' work have been done in lookir up causes of death in NOVS files. This phase of the work has proved to be very time consuming, and a few more months will be required to complete the task.

(D) Significance to Cancer Research

1) While this study is, in its first stage, similar to the Railroad Retirement Board study, its real significance lies in the prospect of obtaining detailed data through the forward-going study beginning in January 1956. This information will cover, for each cancer death, such items as detailed primary site of tumor, metastasis if any (with sites), method of diagnosis, and histologic type of tumor. The analysis of these data in connection with occupational or regional variations in cancer mortality, as revealed in this or the Railroad Retirement Board study, should add considerably to our understanding of such variations in relation to possible occupational carcinogens.

(E) Proposed Course of Project.

1) The next few months should see the completion of the first stage, namely analysis of the data obtained from existing records. As regar the forward-going phase of this study, just now beginning, a year or two will be required to obtain meaningful results from this phase.

PROJECT REPORT FORM (CONT'D)

NCI-128
SERIAL NO.

BUDGET ACTIVITY:

RESEARCH	[ ]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	TECHNICAL ASSISTANCE	[x]

COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 or 1957.

Brotherhood of Railroad Trainmen
Brotherhood of Locomotive Firemen and Enginemen
National Office of Vital Statistics
Canadian Provincial Offices of Vital Statistics

NO ENTRIES FOR ITEMS 13, 14, 15 & 16

PROJECT REPORT FORM

1. Cancer INSTITUTE	2. Field Investigations and Demonstrations Branch LABORATORY OR BRANCH	NCI-129(C)
3. Field Studies Sections SECTION OR SERVICE	4. LOCATION (IF OTHER THAN BETHESDA)	5. SERIAL NO.

Health Survey of personnel employed in baths at Hot Springs, Arkansas
PROJECT TITLE

P. A. Lawrence and V. Archer
PRINCIPAL INVESTIGATOR(S) Dr. Philip Morgan left this project in July, 1955.

OTHER INVESTIGATORS

PROJECT DESCRIPTION

(A) Objective

To evaluate the cancer experience in a selected occupational group with long-time exposure to increased atmospheric concentrations of radon and its by products.

(B) Methods Employed: This project combines a retrospective and a forward-ing field investigation.

1) The population group for the forward-looking study includes all oyees of 18 bath houses in Hot Springs, Arkansas. These people are under rvision of the National Park Service. They receive periodic and annual physic- xamination. Each employee has been interviewed for pertinent personal and pational data including reproductive history, medical history and personal ts (smoking, etc.). Attempt will be made to follow this group to death.

2) The population for the combined retrospective-forward-looking study estricted to the massage operators who have been employed since 1936. All e having left employment are being traced by social security number, postal arding system and otherwise. All but 4 are now accounted for.

(C) Major Findings

Comparison of 1954 and 1955 annual examinations of Hot Springs Bath House oyees.

NCI-129(c)
SERIAL NO.

PROJECT REPORT FORM (Cont'd)

1) Concerning the stability of the worker population, it is interesting to note that of 359 individuals examined in January of 1955, 293 had been examined during all three of the previous project examinations, that is 1953, 1954 and 1955. Of 359 workers, 23 were examined for the first time in the study during January 1955, 38 were examined during 1954 and 1955 only and 5 were examined in 1953 and 1955 but not during 1954.

2) Sedimentation rate elevations were noted in 123 individuals in 1954 but in only 66 individuals in 1955. Sedimentation rates were considered significantly elevated if above 20 millimeters for males or above 30 millimeters for females. 71% (47 cases) of the 1955 cases had been reported elevated during the 1954 examination.

3) Questionably significant variations in the usual polymorphonuclear leukocyte to lymphocyte ratio were noted in approximately the same number of individuals during both years. There were 67 reversals of some degree in the poly-lymp ratio in 1954 and 65 reversals of some degree during the 1955 examination. 42% (27 cases) of the 1955 cases are repeats from 19[illegible].

4) Blood pressure elevations above 150/90 were found in 43 individuals in 1954 and in 50 individuals in 1955. 54% of the 1955 cases(27 cases) are repeats from 1954.

5) 27 anemias of some degree were noted during the 1955 examination.

(D) Significance to Cancer Research

Insofar as field investigations into etiology of cancer is concerned, this project seems ideal in that it is a naturally-occuring field experiment that was awaiting investigation. It affords an opportunity to study the effects of exposure of human beings to increased and probably constant levels of naturally occurring radon and its decay products. Laboratory experiments with animals have shown that these radioactive substances are carcinogenic.

The experiment is uncomplicated by such factors as heavy industrial air pollution or the handling of a multiplicity of suspected carcinogens as are found in other occupational environments. Results obtained will have importance bearing on other researches in the field of low-level exposure to radioactive substances.

(E) Proposed Course of this Project

1) In February 1956 all active bath house personnel receive another comprehensive physical examination by a contract physician in a contract hospital. These data will be added to the study records.

2) All massage workers will be contacted again in 1956 to ascertain their health status.

PROJECT REPORT FORM (Cont'd)

129 (c)
AL NO.

(E) Proposed Course of this Project (Cont'd.)

3) Continuing efforts will be made to discover information about the persons yet missing from the study.

4) Additional environmental data will be collected.

(F) Patient Material

Past and present personnel employed in baths at Hot Springs.

PROJECT REPORT FORM (Cont'd)

NCI-129 (c)
SERIAL NO.

11. BUDGET ACTIVITY:

RESEARCH ☐ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☒

12. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 or 19

National Park Service.

13. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

None.

NO ENTRIES FOR ITEMS 14, 15 & 16.

PROJECT REPORT FORM

Cancer	2. Field Investigations & Demonstrations Branch	
INSTITUTE	LABORATORY OR BRANCH	
Field Studies Sections	4.	5. NCI-130
SECTION OR SERVICE	LOCATION (IF OTHER THAN BETHESDA)	SERIAL NO.

Survey of Cancer Mortality in West Virginia
PROJECT TITLE

P. A. Lawrence
PRINCIPAL INVESTIGATOR (S)

B. C. Ingraham, II
OTHER INVESTIGATORS

PROJECT DESCRIPTION

(Because of lack of statistical-clerical time, this project is being held in abeyance for completion at a later date. It is considered well worth pursuing further. Also, however, it probably will not suffer by inactivation for a time as would other projects that have active cooperation and interest of persons outside the Public Health Service. All basic data for this study are in hand at Bethesda.)

(A.) Objectives.

1) To determine any significant differences in the distribution of cancer mortality rates between the counties in a single, selected state and to search for possible reasons for any observed differences.

(B.) Methods Employed

1) Review and collection of vital statistics records for cancer deaths occurring over a 12 year period. Classification, grouping, enumeration of the data and computation of various rates adjusted for such factors as age, sex, race and occupation is being done.

2) In the counties showing significantly different (high or low) rates for specific cancer sites, more detailed study will be planned of such local factors on industry, topography, air pollution, and characteristics and habits of the population.

PROJECT REPORT FORM (Cont'd)

NCI-130
SERIAL NO.

3) Leads developed by study of local factors will be followed further by the direct approach to suspected sources of potential carcinogens. Detailed inquiry among small, selected population groups will be exploited with respect to cancer experience and environment.

(C) Major Findings

1) One set of data covering cancer deaths for all sites for 1946-1947 indicates a higher than expected occurrence of primary cancer of the liver and biliary system.

2) Another set of data covering all deaths from cancer of the lung for the period 1940-1951 inclusive showed statistically significant differences in rates between counties.

3) A third set of data covering all lung cancer deaths among West Virginia residents (including those who died out of state) in 10 years yielded 8 counties with rates sufficiently high to be worthy of specific investigation.

4) Occupational classification of death certificates for the 12 year study period reconfirmed an impression that lung cancer seems to occur with increased frequency in persons working with metals.

5) Because of precedence in urgency of other projects, further work on this project is being held in abeyance. However, all basic data have been collected, tabulated and studied to some extent.

(D) Significance to Cancer Research

1) Nickel is a suspected carcinogen and West Virginia contains the only major nickel refinery in the United States.

2) The county in which the refinery is located did show a significantly higher lung cancer rate than the rest of the state. Death certificate data are insufficient to even suggest that the nickel plant may be responsible for the increased cancer deaths: -- other factors can be explored only on a local level.

3) More reliable information on cancer incidence in general and on lung cancer in particular are needed to help detect the environmental factors which may be related to its cause. Similar state-wide cancer mortality studies in the United States have been published but they have usually been confined to shorter base periods (5 years or less). The present 10-12 year study should yield more stable statistical information.

PROJECT REPORT FORM (Cont'd)

E) Proposed Course of Project

1) As soon as personnel time allows, a report of this statistical study is to be prepared. Based on the report, appropriate local investigations will be planned in individual counties or other subdivisions to pursue further any possible environmental causes of increased or decreased cancer rates. It is believed that possible carcinogenic factors can be explored only on a local project basis.

PROJECT REPORT FORM (Cont'd)

10. NCI-130
SERIAL NO.

11.

BUDGET ACTIVITY:

RESEARCH	☐	ADMINISTRATION	☐
REVIEW & APPROVAL	☐	TECHNICAL ASSISTANCE	[x]

NO ENTRIES FOR ITEMS 12, 13, 14, 15 & 16.

PROJECT REPORT FORM

1. Cancer INSTITUTE
2. Field Investigations & Demonstrations Branch LABORATORY OR BRANCH
3. Field Studies Sections SECTION OR SERVICE
4. LOCATION (IF OTHER THAN BETHESDA)
5. NCI-131 SERIAL NO.

6. Geographic Distribution of Respiratory Cancer Mortality in 15 Selected States PROJECT TITLE

7. P. Lawrence, E. Young PRINCIPAL INVESTIGATOR(S)

8. S. C. Ingraham, II, M.D. OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

(A) Objective

To discover geographic locations of any areas within fifteen (15) selected States which might be experiencing unusual mortality rates due to pulmonary cancer.

(B) Methods Employed

1) Special tabulations covering a ten-year period were obtained from the National Office of Vital Statistics. Analysis will be made of all cancer deaths due to oral and pulmonary cancer occurring among residents of the selected States by year, county, race, sex, and age. The States included are: West Virginia, Virginia, Maryland, Pennsylvania, Ohio, Kentucky, and North Carolina; Missouri, Arkansas, and Louisiana; Arizona, Utah, Colorado, New Mexico, and Montana.

2) Computations to be made include age-specific rates by State, county, site, sex, and race. Age-adjusted rates will be computed for inter-state and inter-regional comparison. Ratios of observed to expected cases based on State rates will be used for intra-State comparisons by county. Standard tests for significance of differences will be applied in cooperation with the Biometrics Section of National Cancer Institute.

(C) Major Findings

No major findings at this time. However, some interesting and statistically significant geographical differences are developing.

NCI-131
SERIAL NO.

PROJECT REPORT FORM (Cont'd)

(D) Significance to Cancer Research

With full realization of the shortcomings of cancer mortality data based upon death certificates, nevertheless, it is believed that the body of information being developed in this project will serve a number of useful purposes in the search for etiological agents in the human population. For example, geographical patterns may evolve to suggest new leads for detailed field investigations and experiments designed to explai marked differences in observed lung cancer rates; the data are already serving in tests of previously announced impressions and hypotheses based on short-term observations; they will provide handy reference material as new leads are developed in experimental laboratories, and finally, they will be highly desirable as a baseline against which to compare future information.

(E) Proposed Course of Project

This project was slowed down by shortage of personnel during 1955. data necessary to the study is in Field Studies Sections office. This project should be finished during 1956. However, significant findings ma be followed into later years, and it may be desirable to purchase similar data for other cancer sites in other States.

PROJECT REPORT FORM (Cont'd)

0. NCI-131
SERIAL NO.

1. BUDGET ACTIVITY:

RESEARCH	/_/	ADMINISTRATION	/_/
REVIEW & APPROVAL	/_/	TECHNICAL ASSISTANCE	/X/

2. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 or 1957:

None

3. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

None.

0 ENTRIES FOR ITEMS 14, 15 & 16.

PROJECT REPORT FORM

Cancer | 2. Field Investigations & Demonstrations Branch
INSTITUTE | LABORATORY OR BRANCH

Field Studies Sections | 4. Bethesda, Maryland | 5. NCI-132
SECTION OR SERVICE | LOCATION (IF OTHER THAN BETHESDA) | SERIAL NO.

Cancer experience in community population exposed to unusual radon gas concentration.
PROJECT TITLE

Pope A. Lawrence; Dr. V. Archer; Philip Morgan (left this project July 1, 1955)
PRINCIPAL INVESTIGATOR(S)

Because of lack of Field Investigator time this project was held in abeyance for the majority of this year. It is considered well worth pursuing further. In November Asst. San. (R) Henry Greenville was added to the Field Studies Sections staffs. His presence makes possible reactivation of this project for 1956.
OTHER INVESTIGATORS

PROJECT DESCRIPTION

(A) Objectives

This is one of several related field study projects being conducted to determine possible association between occurrence of cancer in human population groups and long time exposure to elevated atmospheric concentration of naturally occurring radioactive substances.

(B) Methods Employed

1) Environmental data with respect to atmospheric concentration of airborne radioactive substances in the study area have been collected by grab-type sampling flasks and assayed by the Occupational Health Program Field Station at Salt Lake City, Utah. Additional samples have been taken and assayed in another laboratory, and other samples will be collected and assayed on the spot using more recently developed field sampling and measurement methods.

2) Biometrical evaluation is to be made of long time cancer mortality data being obtained from the National Office of Vital Statistics and the Arkansas State Vital Statistics Office. This information will be compared to cancer deaths expected if National or State average cancer death rates (corrected for age, etc.) were to apply.

NCI-132
SERIAL NO.

PROJECT REPORT FORM (Cont'd)

(C) Major Findings

Data available permit of only tentative impressions:

1) The atmospheric concentration of radon in many spots in the study community may well be several times the maximum permissible concentration presently recommended by the National Committee on Radiation Protection.

2) Examination of cancer mortality data tabulated for a ten year period established that reported respiratory cancer occurs at a higher rate in the study county (Garland) than in Arkansas as a whole. In the period 1939 to 1948 the average annual respiratory cancer mortality rate (age adjusted) for the county was twice that for the state.

(D) Significance to Cancer Research

1) This study is providing data relative to the possible role of naturally occurring ionizing radiation and human cancer. If it yields sound impressions which can be duplicated from other localities, then an important step will have been taken toward one rational explanation of apparent geographical variation in occurrence of some cancers.

2) Knowledge accumulated with respect to possible effects of atmospheric concentration of radioactive substances in the community under study will be of value in future consideration of maximum permissible concentration of radioactive substances that may be released into the environment.

(E) Proposed Course of Project

1) Continuing collection of atmospheric radioactivity data in the study community and county.

2) Continuing collation and biometric analysis of cancer mortality records for cancer of all sites for selected counties in Arkansas and for the State as a whole; through cooperation of the State Health Department and the National Office of Vital Statistics.

3) As appropriate, local environmental and population data and pertinent specific data on reported cancer deaths in the area are being and will continue to be gathered by staff personnel to whom this project is assigned.

PROJECT REPORT FORM (Cont'd)

NCI-132
SERIAL NO.

BUDGET ACTIVITY:

RESEARCH	/ /	ADMINISTRATION	/ /
REVIEW & APPROVAL	/ /	TECHNICAL ASSISTANCE	/X/

COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 or 1957.

Arkansas State Department of Health.

IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

None.

ENTRIES FOR ITEMS 14, 15 & 16.

PROJECT REPORT FORM

Cancer	2.	Field Investigations & Demonstrations Branch	
INSTITUTE		LABORATORY OR BRANCH	
ield Studies Sections	4.	Boston, Massachusetts	5.NCI-133 (C)
ECTION OR SERVICE		LOCATION (IF OTHER THAN BETHESDA)	SERIAL NO.

Study of Lymphoma Cases treated in a Selected Hospital in New England, Including
ROJECT TITLE Observations on Patients and Record.

r. John B. Vander
PRINCIPAL INVESTIGATOR(S)

r. S. C. Ingraham, II
OTHER INVESTIGATORS

ROJECT DESCRIPTION

A survey of environmental and clinical factors common to patients with lymphoma
(A) Objectives.

To obtain data relative to environmental, medical, person, and family factors that may be associated to a greater degree than normal for patients developing lymphoma. It is designed to serve as a corallary study to that being carried on with children at another hospital. In this case, however, an adult population will be used but with the same emphasis on history of exposure to chemicals and history of allergy.

Methods Employed.

Preliminary phases of the study will consist of two parts as follows:

1) Review of records for the past two years of patients admitted to the hospital with lymphoma, for the purpose of determining factors which may be commonly associated with this disease.

2) The study of patients currently being treated, with additional emphasis on environmental and occupational histories, to elicit factors that may have a common basis in this group. Patient material: - All patients with lymphoma admitting to a large teaching hospital (approximately 450 beds, in a New England area).

Major Findings.

Preliminary survey indicates that records are very complete, diagnostic facilities are excellent, and diagnoses almost invariably are confirmed by tissue

PROJECT REPORT FORM (Cont'd)

NCI-133 (c)

study. Except for these findings, there are no findings in regard to the study since it is just now developing.

(D) Significance to Cancer Research

With the exception of x-radiation and with the exception of vague repor on benzol exposure, environmental factors which are common to groups of patients afflicted with lymphoma are not known. Such data are of importance in any attempt to elicit the etiologies of this disease, since it is recog nized that any information on causitive factors have a marked practical effec in preventive measures which may be taken, and since no curative therapy is available.

(E) Proposed Course of Project.

The study will be develop along plans outlined, and any specific leads developed will be followed-up. It is not possible at this moment to predict in what direction the major emphasis will be placed, since the study is in reality a broad investigation aimed at determining specific fields of en- deavor that might be profitable for further study.

(F) Patient Material

All cases of lymphoma seen at a selected New England Hospital.

PROJECT REPORT FORM (Cont'd)

NCI-133 (c)
SERIAL NO.

BUDGET ACTIVITY:

RESEARCH	☐	ADMINISTRATION	☐
REVIEW & APPROVAL	☐	TECHNICAL ASSISTANCE	☒

COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 or 1957.

None

IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

This project is very similar to the environmental studies being conducted at Children's Hospital by Dr. Manning on the parents of children who have developed leukemia.

NO ENTRIES FOR ITEMS 14, 15 & 16.

PROJECT REPORT FORM

Cancer	2.	Field Investigations & Demonstrations Br.	
INSTITUTE		LABORATORY OR BRANCH	
ield Studies Section	4.	Boston, Mass	5.NCI-134(c)
ECTION OR SERVICE		LOCATION (IF OTHER THAN BETHESDA)	SERIAL NO.

ancer Incidence in a population of 5000 persons examined periodically.
PROJECT TITLE

. Vander
PRINCIPAL INVESTIGATOR(S)

)r. Baum
)THER INVESTIGATORS

?ROJECT DESCRIPTION

(A) Objectives.

1) To determine the incidence of cancer of major sites in a selected population under continuing and regular medical observation.

2) To inquire into possible etiologic factors of any unusual increase or decrease of cancer incidence (as compared to general population data) in the study population.

(B) Methods Employed.

1) The population numbering about 5000 persons has been receiving biennial physical examinations with emphasis on detection of early signs of heart disease. The present project represents an intensification of emphasis on search for cancers that are accessible to direct examination. Such cancers are known to represent more than 50% of all cancers.

2) There is, of course, prompt follow-ups on individuals of the study group found at examination to have symptoms or signs of less accessible disease.

(C) Major Findings.

1) A group of approximately 100 solitary nodules of the thyroid gland have been discovered, of which 10% have been removed by surgery. The remainder will be kept under observation to determine subsequent changes. This study This study group has been kept under surveillance during 1955.

PROJECT REPORT FORM (Cont'd)

NCI-134
SERIAL NO.

(D) Significance to Cancer Research

1) Makes available more data on occurrence of cancer in a selected, well deliniated group of statistically workable size.

2) In particular will provide information about the frequency of malignancy in solitary nodules of the thyroid gland.

3) This well documented, forward-looking study is expected to furnish a needed test of the usefulness of occupational history data in predicting possible environmental influences on occurrence of cancer.

(E) Proposed Course of Project

1) In line with previously established procedures, one-half of the population group will be examined annually.

2) Any cancer discovered will be treated and the patients will be marked down for particular follow-up.

(F) Patient Material

Five thousand presumably healthy people living in a New England city. This is the same group which is being examined periodically by the National Heart Institute.

PROJECT REPORT FORM (Cont'd)

NCI-134 (c)
SERIAL NO.

BUDGET ACTIVITY:

RESEARCH	/7	ADMINISTRATION	/7
REVIEW & APPROVAL	/7	TECHNICAL ASSISTANCE	X

COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 or 1957:

National Heart Institute.

IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

This project complements a study by NHI on the same group of people, the two groups investigating different diseases.

NO ENTRIES FOR ITEMS 14, 15 & 16.

PROJECT REPORT FORM

1. Cancer INSTITUTE	2. Field Investigations & Demonstrations Br LABORATORY OR BRANCH
Field Studies Sections SECTION OR SERVICE	4. Providence, R. I. LOCATION(IF OTHER THAN BETHESDA)
	5. NCI-135 SERIAL NO.

Frequency of Occurrence of Cancer and Other Major Diseases Among a Group covered by a State-wide Unemployment Insurnace
PROJECT TITLE

Dr. J. Vander, Dr. H. Dorn
PRINCIPAL INVESTIGATOR(S)

B. E. Carroll, Pope Lawrence
OTHER INVESTIGATORS

PROJECT DESCRIPTION

(A) Objectives

The objective of this project is to determine the prevalence, and if possible to obtain incidence rates on the occurrence of cancer of the major sites among selected occupational groups.

(B) Methods Employed.

In one State, unemployment insurance covers a population group ranging roughly from 236,000 to 300,000. Insurance is compulsory for all persons who ordinarily come under social security regulations; that would be most persons working in establishments employing four or more persons. Female workers make up 42 percent of this total, and account for much of the fluctuation in the total size of the group.

Monthly reports of all primary malignancies of the lung and respiratory tract have been collected by Dr. Vander since the month of July 1953. Since July 1953 all disabilities occurring in this population group have been coded by the "International Classification of Disease," in three digits. Cases reported to date include social security number, age, sex, morbidity code and a brief occupational history.

After review of the problem, it was decided that cancer of all sites and major diseases would be collected in this manner. It was estimated by Dr. Dorn that reasonable population figures could be estimated from the census of the State for the groups desired. In addition, on each case of lung cancer, an occupational history is being obtained by an interviewer from the Unemployment Compensation Commission Office, in conjunction with Dr. Vander.

PROJECT REPORT FORM (CONT'D)

NCI-135
SERIAL NO.

(C) Major Findings.

None. The study was started late in 1955.

(D) Significance to Cancer Research

With very few exceptions, no incidence rates for cancer or other diseases are available on localized occupational groups. Precise information on these points would have definite bearing on further study of the etiologies of those cancers believed to be or questionably considered to be of environmental origin. Further progress in the field of environmental cancer can be obtained only by the collection of such data as described above.

(E) Proposed Course of Project.

Start of the project was delayed for the completion of administrative details but is now under way. After about one year's interviews have been collected, it is expected that preliminary results can be obtained. Additional time may be necessary to secure meaningful results, particularly if differences in cancer prevalence among various groups are not very great.

PROJECT REPORT FORM (Cont'd)

NCI-135
SERIAL NO.

BUDGET ACTIVITY:

RESEARCH	/ /	ADMINISTRATION	/ /
REVIEW & APPROVAL	/ /	TECHNICAL ASSISTANCE	/X/

COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 or 1957

Office of Biometry of the National Institutes of Health

The Unemployment Compensation Commission of a New England State.

IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

This study is somewhat similar to the study of the uranium miners to determine the incidence of respiratory cancer in that group, as conducted by the Field Investigations and Demonstrations Branch, the Atomic Energy Commission, the Division of Occupational Health. It would complement the study on absenteeism done by the Division of Occupational Health. Apart from these, I believe there are no other similar studies, and there are none of this specific type.

NO ENTRIES FOR ITEMS 14, 15 & 16.

PROJECT REPORT FORM

ancer 2. Field Investigations & Demonstrations B
INSTITUTE

ield Studies Sections 4. Oklahoma City, Oklahoma 5. NCI-136
ECTION OR SERVICE LOCATION (IF OTHER THAN BETHESDA) SERIAL NO

ancer Incidence in Selected Population Groups in Alabama
PROJECT TITLE

r. Philip Morgan (left FIDB 6/30/55), P. Lawrence
RINCIPAL INVESTIGATOR(S)

r. S. C. Ingraham, Dr. H. Dorn
THER INVESTIGATORS

ROJECT DESCRIPTION

(A) Objective

To determine the frequency of occurrence of cancer of different sites among selected population groups.

(B) Methods Employed

From a list at hand of over 750 employees of various units (as of the year 1947) a study was made during 1955 from the State's Vital Statistics Department and other registries to determine the number of persons in this group who have expired and the causes of their deaths. To confirm accuracy of the original list and to assure that the individual belonged to one of the groups under study, the main occupation as noted on each death certificate was checked at the time of abstracting it. In this manner the frequency of occurrence of cancer of major sites among the population group in question is being sought.

(C) Major Findings

The information for this study has been gathered from vital records and is now in process of biostatistical analysis. Collation of these data is expected to furnish occupation-specific prevalence rates of cancer for the study group.

(D) Significance to Cancer Research

Prevalence and incidence rates in selected occupational groups are available in only very rare instances. Further information upon the etiologies of environmental cancer depend upon the acquiring of such information.

PROJECT REPORT FORM (Cont'd)

NCI-136
SERIAL NO.

(E) Proposed Course of Project.

During the coming year the cancer occurrence rates and statistical reliability of the rates in each population group will be determined. These will be used as leads to suggest further environmental cancer studies in any selected portions of the group where the prevalence appears to be increased.

PROJECT REPORT FORM (Cont'd)

NCI-136
SERIAL NO.

BUDGET ACTIVITY:

RESEARCH	/	ADMINISTRATION	/
REVIEW & APPROVAL	/	TECHNICAL ASSISTANCE	X

COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 or 1957:

None

IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

This resembles a project being conducted by Dr. Vander in Boston, and is similar to the current project being conducted on the Civil Service Commission's cases by the Central Investigating Unit.

NO ENTRIES FOR ITEMS 14, 15 & 16.

PROJECT REPORT FORM

Cancer	2.	Field Investigations & Demonstrations Br.	
INSTITUTE		LABORATORY OR BRANCH	
Field Studies Sections	4.	Bethesda, Md.	5. NCI-137
SECTION OR SERVICE		LOCATION (IF OTHER THAN BETHESDA)	Serial No

Etiology of Lung, Laryngeal and Bladder Cancer in New Orleans, Louisiana
PROJECT TITLE

S. C. Ingraham, II and P. A. Lawrence

Because of lack of field investigator time, this project is being held in abeyance for completion at a later date. It is considered well worth pursuing further. Also, however, it probably will not suffer by inactivation for a time as would other projects that have active cooperation and interest of persons outside the Public Health Service.

OTHER INVESTIGATORS

PROJECT DESCRIPTION

(A) Objective

1) To verify the existence of high occurrence rates of lung, laryngeal and bladder cancer apparent in New Orleans, La. from a study of the 1947 morbidity-mortality records.

2) To seek information relating to the cause of the high level of cancer occurrence in the New Orleans area.

3) To develop and test practical methods of collecting supplementary data in areas previously surveyed in order to evaluate possible reasons for unusually high or low incidence of cancer.

(B) Methods Employed

1) Reported morbidity and mortality information was collected and analyzed biometrically.

2) Over-reporting was minimized by reinvestigating residence status of cases through death certificate inspection, hospital record review, use of city directories and telephone directories and by personal interview of patients, relatives or friends.

3) Review of category assignment of diagnoses by checking original survey records for possible errors in coding, by examination of hospital clinical records for discrepancies between final diagnoses on the hospital records and the survey records and by inspecting death certificates for reported diagnoses.

PROJECT REPORT FORM (Cont'd)

NCI-137
SERIAL NO.

(B) Methods Employed (Cont'd)

4) To seek information pertinent to the cause of the high cancer occurrence rate in the New Orleans area special attention was directed in a selected study group, to additional collection of detailed family medical histories, occupational histories, unusual environmental circumstances, geographical distribution of cancer cases within the city limits of New Orleans, and possible presence of air pollutants or smog.

(C) Major Findings

1) The increased occurrence rates of cancer of the lung, larynx and bladder in New Orleans cannot be explained away as an artifact on the basis of: (a) nonresidency of any great proportion of the cases, (b) errors in coding or reporting of the cases.

2) Even when the New Orleans figures are corrected for nonresidency and coding errors, the lung, larynx and bladder cancer rates remain higher than those of 9 other cities whose records were examined. It should be noted that New Orleans retains first place even though the data for the other areas was not corrected for errors of residency and coding.

3) No leads were discovered in the small group of families interviewed personally for occupational and environmental histories.

4) There was no observable geographical grouping of cases within the New Orleans area.

5) For guidance in future similar studies the following information was gained:

(a) Prior to coding and analysis, the original survey cards should be reviewed carefully to determine which cases have diagnoses established beyond question and which cases should be reviewed carefully prior to their inclusion in the study. (i.e. DIAGNOSIS SHOULD BE CONFIRMED BEFORE BIOMETRIC ANALYSIS OF THE DATA).

(b) Local medical societies and practicing physicians should have the project explained fully so their cooperation may be solicited directly and their reservation regarding the procedures discovered promptly.

(c) Time lapse between an original survey and the follow-up study should not be so long that hospital and other records are difficult to obtain access to and that cases and/or relatives may be difficult to trace.

(d) Unless a person has followed a single occupation throughout his lifetime the family and the hospital records usually cannot reveal his occupational history with any degree of accuracy.

PROJECT REPORT FORM (Cont'd)

I137
RAL NO.

(D) Significance to Cancer Research

This project is a logical follow-up procedure on field researchers in cancer already accomplished. Through it the fact of increased cancer already accomplished. Through it the fact of increased cancer occurrence of certain sites in the New Orleans area has been confirmed. Negative evidence for selected possible reasons for the increased rates has been gained and procedural information that will be most useful in future cancer field studies has been gained.

(E) Proposed Course of the Project

On-the-spot activities in the New Orleans area have been completed for the present. The data obtained have been collated and considered. This project is in abeyance pending accession of a Field Investigator to continue it.

Similar investigation of other of the 10 cities in the Ten City Cancer Mlrbidity-Mortality Survey is being contemplated in funds and personnel allow.

Environmental and air pollution data in New Orleans are being collected by other activities of the Public Health Service. When reports on the findings of these activities become available, these data will be collated with our cancer study data in search of possible causes for the observed elevation cancer occurrence in New Orleans.

PROJECT REPORT FORM (Cont'd.)

NCI-137
SERIAL NO.

10. BUDGET ACTIVITY:

RESEARCH	[ ]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	TECHNICAL ASSISTANCE	[X]

11. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 or 19

12. None

IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

None

NO ENTRIES FOR ITEMS 13, 14, 15 & 16.

PROJECT REPORT FORM

ancer 2. Field Investigations and Demonstrations Branch
INSTITUTE LABORATORY OR BRANCH

ield Studies Section 4. Oklahoma City, Oklahoma 5. NCI-138
ECTION OR SERVICE LOCATION (IF OTHER THAN BETHESDA) SERIAL NO.

tudy of Occupational Histories of a selected group of patients with cancer of
ROJECT TITLE the skin.

. Morgan (left FIDB 6-30-55). This project was abandoned in 1955 because the
RINCIPAL INVESTIGATOR(S) principal investigator left FIDB and because
dentical work in the same populations is being done on a larger scale under an
NCI Grant at the University of Oklahoma Medical School.

THER INVESTIGATORS

ROJECT DESCRIPTION

(A) Objective.

1) Identification of environmental or occupational factors in a selected State that may be causes or contributory factors in the occurrence of cancer of the skin.

2) Study of selected skin cancer patients for predisposing factors in occurrence, recurrence or repeated occurrence of cancer of the skin.

PROJECT REPORT FORM

ancer NSTITUTE | 2. Field Investigations and Demonstrations Branch LABORATORY OR BRANCH

ield Studies Section ECTION OR SERVICE | 4. Boston, Mass. LOCATION (IF OTHER THAN BETHESDA) | 5. NCI-139(c) SERIAL NO.

tudy of Etiologic Factors in Mothers of Children with Lymphomata (Excluding Leukemia)
ROJECT TITLE

r. Miriam Manning
RINCIPAL INVESTIGATOR(S)

. F. Kaiser, M.D.
THER INVESTIGATORS

PROJECT DESCRIPTION

(A) Objective.

1) This study was listed in 1954 as included in NCI-116. Findings in 1955 have made it desirable to separate NCI-116 into a "leukemia" project, a "lymphomata" project, and an "other cancer" project. This is the "lymphomata" project.

2) To determine whether medical history and environmental factors in mothers of children with lymphomata (other than leukemia) are similar to or different from those of mothers of children with leukemia and with other malignancies (other than lymphomata).

3) To discover etiological factors in lymphomata of childhood.

4) To develop a lymphomata control group for other studies.

(B) Methods Employed.

1) A question sheet was developed which includes pertinent data concerning both the mother and the child.

2) Mothers of children (ages 0-14 years) having lymphoma are interviewed early in the course of the child's disease. Particular care is taken not to relate the questions to the child in such a way as to disturb the mother; and similar questions are asked about other siblings.

PROJECT REPORT FORM (Cont'd)

NCI-139(c)
SERIAL NO.

(B) Methods Employed(Cont'd)

3) Hospital records of the mother are reviewed if they contain data pertinent to the question sheet.

4) Industrial exposures are followed-up where practicable.

5) Material from question sheets is collated and studied, for factors common to the several cases.

(C) Major Findings

1) The most important findings in the results so far tabulated is that mothers of children with lymphomata resemble closely (as far as allergy) those of children with acute leukemia, and differ from those of children with other malignancies of childhood.

(D) Significance to Cancer Research

1) The uncovering of an allergy background in mothers as a factor common to children with leukemia or lymphomata further binds together lymphomata and leukemia and implies there may be a common etiological factor for these diseases. It separates these diseases from the other malignancies of childhood.

2) Expectation is that further tabulations will show other separating factors which may help suggest possible etiology for other malignancies of childhood.

(E) Proposed Course of Project

1) To continue gathering data until significant numbers of lymphoma cases are compiled.

2) To tabulate and analyze data accumulated.

3) Possibly to extend the work to include adults with lymphomata.

(F) Patient Material

Mothers of children with lymphoma who are seen in one of three different Hospitals or clinics in a New England city. Two control groups are maintained--one by interviewing mothers of children who are neighbors to the child with lymphoma, and one by interviewing mothers of children who are ill of some disease other than lymphoma who are in the same hospital.

PROJECT REPORT FORM (Cont'd)

NCI-139(c)
SERIAL NO.

BUDGET ACTIVITY:

RESEARCH	☐	ADMINISTRATION	☐
REVIEW & APPROVAL	☐	TECHNICAL ASSISTANCE	☒

COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 or 1957:

Children's Hospital, Boston, Mass.
Children's Cancer Research Foundation, Boston, Mass.
Children's Medical Center, Boston, Mass.

IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

None.

NTRIES FOR ITEMS 14, 15 & 16.

PROJECT REPORT FORM

Cancer — INSTITUTE
2. Field Investigations & Demonstrations Br. — LABORATORY OR BRANCH

Field Studies Sections — SECTION OR SERVICE
4. Boston, Massachusetts — LOCATION (IF OTHER THAN BETHESDA)
5. NCI-140(C) — SERIAL NO.

Electrophoresis and fluorescence of white blood cells as a possible leukemia diagnostic or screening test.
PROJECT TITLE

John B. Vander
PRINCIPAL INVESTIGATOR(S)

Pope A. Lawrence
OTHER INVESTIGATORS

PROJECT DESCRIPTION

(A) Objectives

To attempt to develop a diagnostic or screening test for the leukemias using paper electrophoresis.

(B) Methods Employed

White blood cells are obtained from patients with various types of leukemia as well as non-leukemic persons. They are freed as much as possible from red blood cells and serum and caused to hydrolyze using various agents such as distilled water, alkalies and perchloracetic acid. The residual fluid is analyzed for fluorescent materials on a paper electrophoresis instrument.

(C) Major Findings

Work to date indicates that there may be a characteristic electrophoretic pattern which will distinguish between lymphatic leukemia, myelogenous leukemia and normal white blood cells.

(D) Significance to Cancer Research

1) This might provide a rapid diagnostic test for leukemia. It might differentiate between such conditions as leukemia, aplastic anemia, aleukemic leukemia, myeloid metaplasia and polycythemia vera.

PROJECT REPORT FORM (Cont'd)

NCI-140(c)
SERIAL NO.

2) Such differentiation is essential to correct treatment.

(E) Proposed Course of Project

Work so far indicates that characteristic electrophoretic patterns for the leukemias may exist. Results are not consistent however and further work remains to be done in standardizing the procedure and using various types of hydrolyzing agents.

(F) Patient Material

Selected leukemic and non-leukemic patients admitted to a New England Hospital.

PROJECT REPORT FORM (Cont'd)

NCI 140(c)
SERIAL NO.

10.

BUDGET ACTIVITY:

RESEARCH	/7	ADMINISTRATION	/7
REVIEW & APPROVAL	/7	TECHNICAL ASSISTANCE	X/7

11.

COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 or 1957:

None

12.

IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

None

NO ENTRIES FOR ITEMS 13, 14, 15 & 16.

PROJECT REPORT FORM

1. Cancer — INSTITUTE
2. Field Investigations & Demonstrations Br. — LABORATORY OR BRANCH
3. Field Studies Sections — SECTION OR SERVICE
4. Boston, Massachusetts — LOCATION (IF OTHER THAN BETHESDA)
5. NCI-141(c) — SERIAL NO.
6. Cancer of Breast as related to lactation, pregnancies and hormone therapy — PROJECT TITLE
7. Dr. John B. Vander — PRINCIPAL INVESTIGATOR(S)
8. Dr. R. F. Kaiser — OTHER INVESTIGATORS
9. PROJECT DESCRIPTION

(A) Objectives

1) To attempt to answer the question of whether or not hormonal treatment of cancer of the breast prolongs life.

2) To study the relationship of lactation, use of estrogens, nursing of offspring, number of pregnancies and marital status to carcinoma of the breast.

3) To study the question: Is there a common denominator in male and female carcinoma of the breast?

(B) Methods Employed

1) This study in its preliminary phase consists of plans for review of records for the past five year period with the purpose of collecting data pertinent to the above points. Records are those from a large New England teaching hospital of approximately 450 beds.

2) Additional data will be obtained by interviews and follow-up of the patients as found to be necessary.

(C) Major Finds

1) At the present time there is no organized scientific evidence that hormonal treatment of breast cancer prolongs life. If significant data can be obtained relative to this it would aid in deciding the proper place of hormones in therapy. Should they be used prophylactically in an attempt to prolong life or reserved for symptomatic treatment as the indications arise.

PROJECT REPORT FORM (Cont'd)

NCI-141(c)
SERIAL NO.

2) There is some reason to believe that the use of estrogens to suppress lactation may be related to the development of breast cancer.

(D) Significance to Cancer Research

Data as outlined above might centribute significantly to the problem of the best hormonal control of cancer as well as to prevention especially in regard to the promiscuous use of estrogens.

(E) Proposed Course of Project

In the large teaching hospital where the records will be examined is a very active breast cancer clinic as well as thyroid clinic. At the present time the principal investigator is engaged in doing active clinical work in both these clinics and is familiar with the patients and records.

The study, it is anticipated, will have three divisions:

(1) Study of survival times of patients who received hormonal therapy versus those who did not.

(2) Comparison of Cancer rates in patients who have a history of use of estrogens before the development of breast cancer with those who did not. This will also apply to lactations, nursing and marital status.

(3) Study of common factors in male and female patients with breast cancer.

(F) Patient Material

The initial part of the study will use the records of selected patients from a New England hospital who have had breast cancer. It is planned that these patients and future breast cancer patients at this hospital will be interviewed as necessary and followed for as long a period as necessary to achieve the objectives of the study.

PROJECT REPORT FORM (Cont'd)

41(c)
SERIAL NO.

BUDGET ACTIVITY:

RESEARCH	/ /	ADMINISTRATION	/ /
REVIEW & APPROVAL	/ /	TECHNICAL ASSISTANCE	/X/

COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 or 1957

None

IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

None

NO ENTRIES FOR ITEMS 13, 14, 15 & 16

PROJECT REPORT FORM

ancer
INSTITUTE

2. Field Investigations & Demonstrations Br.
LABORATORY OR BRANCH

Fild Studies Sections
SCTION OR SERVICE

4. Berkeley, Calif.
LOCATION (IF OTHER THAN BETHESDA)

5.NCI-142
SERIAL NO.

Ealuation of Death Certificate Reliability as Source of Environmental Cancer Information.
POJECT TITLE

Jcn E. Dunn, Jr., M.D.
PINCIPAL INVESTIGATOR(S)

3.
CHER INVESTIGATORS

PJJECT DESCRIPTION

(.) Objective

1) To determine the usefulness of occupational entry on death certificates as a means of developing hypotheses as to increased cancer risks associated with specific occupations.

( ) Methods Employed

1) The availability of a collection of data including detailed life time occupational histories on a group of lung cancer patients (most of whom have since died) made it possible to study the agreement between occupational entry on death certificates and life time occupational histories. Results of this analysis were sufficiently encouraging to warrant pursuing such a study.

2) A study using this method was established in which occupational coding of male deaths between the ages of 35 and 64 for the years 1949 and 1951 is being done. Coding of 1950 deaths had already been done by the National Office of Vital Statistics and a duplicate deck of punch cards was made available for this study.

(:) Major Findings

1) Analysis of the degree of agreement between occupational entry on death certificates and actual occupational history showed that a little less than half agreed on any basis of occupational characterization (usual, last, or any five-year occupation). Agreement with last occupation was best and was in the neighborhood of 70 percent. This is fortunate from a technical, although not from an epidemiological, standpoint in that available populations by occupation from the Census are on that basis.

PROJECT REPORT FORM (Cont'd)

CI-142
SERIAL No.

(D) Significance to Cancer Research

1) It is possible that additional increased occupational cancer risks will be identified. This will provide leads for further study to determine specific carcinogenic factors.

2) Control measures may be indicated to reduce occupational exposure to suspected or proven carcinogens.

3) Evaluation of the usefulness of the occupational entry on death certificates as a readily available source of data. To make recommendations for improving this death certificate entry.

(E) Proposed Course of Project

The data when coded will be analyzed. The findings will determine the future direction of this work. A paper on this study is being processed for publication.

PROJECT REPORT FORM (Cont'd)

MI-142
SERIAL NO.

10. BUDGET ACTIVITY

RESEARCH	/_/	ADMINISTRATION	/_/
REVIEW & APPROVAL	/_/	TECHNICAL ASSISTANCE	/X/

11. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 or 1957:

California State Health Department

12. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH.

None

NO ENTRIES FOR ITEMS 13, 14, 15 & 16.

PROJECT REPORT FORM

1. Cancer INSTITUTE
2. Field Investigations and Demonstrations Branch LABORATORY OR BRANCH
3. Field Studies Sections SECTION OR SERVICE
4. Berkeley, Calif. LOCATION (IF OTHER THAN BETHESDA)
5. NCI-143 SERIAL NO.

6. Relationship of Cancer Occurrence and Socio-economic Factors. PROJECT TITLE

7. John E. Dunn, Jr., M.D. PRINCIPAL INVESTIGATOR(S)

8. R. F. Kaiser, M.D. OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

(A) Objective.

Evaluation of socio-economic factors in relation to the occurrence of cancer generally and specific sites.

(B) Methods Employed.

1) Death certificates coded by census tracts were available from the San Francisco Health Department for the years 1950 - 1953.

2) Two sociological studies of San Francisco were available in which census tracts had been classified on three dimensions--Family Status, Social Rank, and Segregation.

3) Sex-age-site specific death rates for San Francisco as a whole were calculated and applied to the appropriate census tract populations to get expected cancer deaths by site and sex. These were compared with observed deaths from tracts grouped according to the socio-economic variables being studied.

(C) Major Findings.

Principal interest centered on the Social Rank and Family Status variables. Significant correlations were found as follows:

1) For males negative correlations were found with Social Rank and cancer of all sites, upper G. I. tract, stomach, and pancreas. There were no positive correlations.

PROJECT REPORT FORM (Cont'd)

NCI-143
SERIAL NO.

(C) Major Findings (Cont'd)

2) For females Social Rank was negatively correlated with cancer of th G. I. tract, stomach, and cervix uteri. The usual positive association for breast cancer was not found.

3) For males Family Status showed some positive association for cancer of the prostate.

4) For females Family Status was positively correlated with cancer of the stomach and pancreas and negatively correlated with cancer of the cervix uteri.

5) The interaction of Social Rank and Family Status is evident for cancer of the stomach where the highest rates for both sexes was in the Low Social Rank-High Family Status areas. This is also true for cancer of the pancreas in females. Cancer of the cervix uteri is concentrated in the Low Social Rank-Low Family Status area.

(D) Significance to Cancer Research.

1) A number of studies of socio-economic factors in relation to cancer have been made--first in England, then Denmark, and more recently in this country. Socio-economic gradients have been found fairly consistent for some sites; less consistent for others. For example, cancer of the breast in females does not show a gradient in our study. There have been other departures from European studies in this country and what dimensions best demonstrate them.

2) In this study three sociological dimensions were considered for measuring gradients. For some sites the interaction of two dimensions appears to indicate they reinforce each other.

(E) Proposed Course of Project.

Data similar to that from San Francisco are now available for Oakland and Los Angeles. It is planned to repeat the study with these data.

PROJECT REPORT FORM (Cont'd)

NCI-143
SERIAL NO.

BUDGET ACTIVITY:

RESEARCH	☐	ADMINISTRATION	☐
REVIEW & APPROVAL	☐	TECHNICAL ASSISTANCE	☒

COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 or 1957:

San Francisco Health Department.

IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

None

NO ENTRIES FOR ITEMS 14, 15 & 16.

PROJECT REPORT FORM

1. Cancer INSTITUTE 2. Field Investigations & Demonstrations Branch LABORATORY OR BRANCH

3. Field Studies Sections SECTION OR SERVICE 4. Memphis, Tennessee LOCATION (IF OTHER THAN BETHESDA) 5. NCI-144 SERIAL NO

6. Neck tumors in AKR mice Following Innoculation of Newborn Mice with AK Leukemic Supernates
PROJECT TITLE

7. Richard A. Malmgren, Anna Dean Dulaney
PRINCIPAL INVESTIGATORS

8. Mary Gideon
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

(A) Objectives

1) To determine the relationship of certain neck tumors in mice to extracts of leukemic tissue.

(B) Methods Employed

1) Tissue extracts were made of tissues taken from mice dying of leukemia

2) Cell free extracts were prepared by centrifugation.

3) Newborn and older mice were injected with the above extracts, then observed for development of neck tumors and leukemia.

4) Tumors produced in this way were examined histologically and used for transfer experiments.

(C) Major Findings

Neck tumors were produced in AKR mice by injection in early hours of life with acellular leukemic extracts from AKR mice. The development of these tumors was not affected by the simultaneous injection of leukemic cell antiserum, or later injection of leukemic cells.

(D) Significance to NCI Program

1) The relationship(if any) of different types of tumors and leukemias is essential to an understanding of cancer.

PROJECT REPORT FORM (Cont'd)

NCI-144
SERIAL NO.

(E) Proposed Course of the Project

Search for an explanation of the mechanism by which cell free leukemic tissue extracts can induce neck tumors in a homologous strain of mice.

PROJECT REPORT FORM (Cont'd)

1. NCI-144
SERIAL NO.

11. BUDGET ACTIVITY:

RESEARCH	☐	ADMINISTRATION	☐
REVIEW & APPROVAL	☐	TECHNICAL ASSISTANCE	☒

12. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 or 1957:

This is a cooperative project between FIDB and the University of Tennessee.

13. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

None known.

NO ENTRIES FOR ITEMS 14, 15 & 16.

PROJECT REPORT FORM

1. Cancer — INSTITUTE
2. Field Investigations & Demonstrations Branch — LABORATORY OR BRANCH
3. Field Studies Sections — SECTION OR SERVICE
4. Memphis, Tennessee — LOCATION (IF OTHER THAN BETHESDA)
5. NCI-145 — SERIAL NO.

6. Liver Mitotic Stimulant present in Tumor Tissue
PROJECT TITLE

7. Dr. Richard A. Malmgren
PRINCIPAL INVESTIGATOR(S)

8. OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives

1) To determine the mechanism by which a localized malignant tumor produces systemic effects.

2) Specifically, to determine whether or not extracts of cancerous tissue will affect the rate of cell division in mouse liver.

(B) Methods Employed

1) Injection of extracts of cancer tissue into normal mice.

2) Comparison of the mitotic activity in the liver cells of the experimental animals and in normals.

(C) Major Findings

It has been shown that when extracts of cancer tissue are injected into normal mice an increased rate of liver cell division results.

(D) Significance to NCI Program

1) Obtaining basic information on the relationship between tumors and their hosts.

(E) Proposed Course of the Project

Continued search into the mitotic stimulating activity of tumor extracts.

PROJECT REPORT FORM (Cont'd)

10. NCI-145
SERIAL NO.

11.
BUDGET ACTIVITY:

RESEARCH	☐	ADMINISTRATION	☐
REVIEW & APPROVAL	☐	TECHNICAL ASSISTANCE	☐

12.
COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE , OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 or

This is a cooperative project between FIDB and the University of Tennessee

13.
IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

None known.

NO ENTRIES FOR ITEMS 14, 15 & 16.

PROJECT REPORT FORM

Cancer INSTITUTE | 2. Field Investigations & Demonstrations Branch LABORATORY OR BRANCH

Field Studies Sections SECTION OR SERVICE | 4. _____ LOCATION (IF OTHER THAN BETHESDA) | 5. NCI-146 SERIAL NO.

Geographic and environmental factors in cancer mortality in Washington County, Md.
PROJECT TITLE

Katherine Beck, B. E. Carroll
PRINCIPAL INVESTIGATOR(S)

Pope A. Lawrence, Henry Greenville
OTHER INVESTIGATORS

PROJECT DESCRIPTION

(A) Objectives

1) To determine geographic patterns of cancer mortality and trends for a period of 30 years in the county.

2) To relate geographic patterns of mortality to environmental factors such as underlying geologic formation, type of soil, water supply, housing, and background radioactivity of soil, water, dwelling houses, pavements, water, etc.

(B) Methods Employed

Field

1) Previous work done by the Public Health Service/Station in Hagerstown has revealed that the population of Washington County, Md. has been remarkably stable for many years.

2) Transcripts of all death certificates for Washington County on which cancer was mentioned are available in the County Health Department covering the period from 1898 through 1954.

3) The residence of each cancer decedent since 1924 will be located as to election district and as to whether inside or outside the city of Hagerstown. Age-adjusted cancer death rates will be computed for each election district in the county, for the city of Hagerstown, and for each district within the city for 10-year periods centered around the census years 1930, 1940, and 1950.

4) From maps owned by the city government, the dwelling of each cancer decedent in Hagerstown will be coded as to age, type of construction, material and roof. From these data the possible association between type of housing and cancer mortality will be studied.

PROJECT REPORT FORM (Cont'd)

CI-146
SERIAL NO.

Methods Employed (Cont'd.):

5) On the basis of geographic patterns discovered and the relation of housing to cancer, if any, more detailed studies will be undertaken of the environmental influences existing in smaller areas such as city blocks or in individual buildings.

(D) Major Findings

None.

(E) Significance to Cancer Research

1) Little work has been done on geographic patterns of cancer for areas smaller than counties or cities. This analysis alone, for a 30-year period, should be a worth-while contribution.

2) Studies done in the Netherlands and England have reported association of geologic formations, types of soil, and composition of drinking water with cancer mortality. Preliminary study on another project of the FSS has indicated the existence of patterns of cancer mortality in the U. S. which coincide to some extent with geographic and geologic features of the areas involved. The present project is designed to throw more light on this problem through intensive study of a single county where population has been stable for a long period of years.

3) Little is known of the effects of long term exposure to very low levels of ionizing radiation on health or on human cancer incidence, although such effects have been generally presumed to be negligible. Little study has been made of local variations in background radiation except in areas of special interest, but a few surveys have shown such variations to be great. Preliminary observations in Washington County have indicated that the background radiation varies widely from place to place. It is hoped that intensive study of subdivisions of this county will give at least tentative answers as to any possible relation between exposure to background radiation and mortality from cancer.

(F) Proposed Course of the Project

1) Preliminary work of checking and coding death certificates is under way, and mortality rates for local areas should be completed in a few months.

2) The studies of environmental influences will require a considerably longer time -- possibly a year or two more.

PROJECT REPORT FORM (Cont'd)

NCI-146
SERIAL NO.

BUDGET ACTIVITY:

RESEARCH	☐	ADMINISTRATION	☐
REVIEW & APPROVAL	☐		☒

COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 or 1957:

Washington County Health Department
PHS Field Station, Hagerstown

IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

None.

ENTRIES FOR ITEMS 14, 15, & 16.

PROJECT REPORT FORM

1. Cancer — INSTITUTE
2. Field Investigations and Demonstrations Branch — LABORATORY OR BRANCH
3. Field Studies Sections — SECTION OR SERVICE
4. Columbus, Ohio — LOCATION (IF OTHER THAN BETHESDA)
5. NCI-147(c) — SERIAL NO.

6. Vaginal and Cervical Cytology as a means of Cancer Case Finding- Columbus, Ohio
PROJECT TITLE

7. Dr. Emmerich Von Haam and Dr. Raymond F. Kaiser
PRINCIPAL INVESTIGATOR(S)

8. Dr. John L. Ullery and Dr. Samuel C. Ingraham, II
OTHER INVESTIGATORS

9 PROJECT DESCRIPTION

(A) Objectives.

1) Relative comparison of vaginal aspiration, cervical scraping, and aspiration of the uterine cervical canal as sources of cytologic test material in case-finding for cancer of the uterus in the adult female population of Columbus, Ohio

2) Evaluation of vaginal aspiration for reliability as a case finding test for cancer of the uterus in the adult female population of Columbus, Ohio.

3) Case-finding for cancer of the uterus in the adult female population of Columbus, Ohio.

(B) Methods Employed.

1) By means of the vaginal smear method and other, medically accepted cancer diagnostic tests and procedures a survey is to be made of the adult female population in Greater Columbus, Ohio for occurrence of Uterine cancer.

2) Cancer cases detected are to be evaluated and treated appropriately by usual accepted medical, radiological and surgical methods.

3) Appropriate clinical and medical-statistical records will be kept to provide adequate patient-follow-up and evaluation of uterine cancer occurrence, incidence of false negative and false positive case-finding results, and efficiency of the several case-finding and diagnostic methods.

PROJECT REPORT FORM (Cont'd)

NCI-147(c)
SERIAL NO.

Methods Employed (Cont'd)

4) This study will consist of two interrelated but physically distinc operations:

a) Relative evaluation of case-finding and diagnostic techniques:- in this portion of the study emphasis will be placed upon the thoroughness with which a randomly selected, large group of patien are examined. Here the methods of exfoliative cytology to be employed are the taking of a vaginal smear according to a standard technique, plus the taking of cervical scrapings and cervical aspiration after exposure of the cervix by speculum. Inspection and description of the cervix will also be recorded by the examin physician or medical student. The several laboratory specimens will be examined and evaluated separately and the finding of the several methods collated, correlated, compared, and analyzed.

b) Case finding for relative occurrence of uterine cancer in age- specific, national-origin-specific and other specific population segments: — in this portion of the study emphasis will be placed upon offering vaginal aspiration exfoliative cytology to large population segments on a periodic recall basis, specific diagnosi by accepted clinical and laboratory methods, and appropriate ther y of all patients found to have uterine cancer. Patient records wi be analyzed biostatistically for incidence, prevalence and other pertinent factors concerning uterine cervical cancer, its detecti and treatment in an adult female population.

(C) Patient Material.

Patient material is to be the adult, female population of Greater Colu Ohio, including clinic and hospital patients, indigent patients, patie of private physicians, industrial workers, and the presumably healthy female population of the area.

(D) Major Findings

None. This study was initiated in December, 1955. Expectation is tha appreciable numbers of patients will be being processed by the end of the first quarter of the year, 1956.

(E) Significance to NCI Program.

1) Collection and collation of further data on course of development, incidence, prevalence, treatability and other pertinent facts about human uterine cervical cancer.

2) Evaluation of effectiveness of exfoliative cytology in case-findi for uterine cervical cancer.

PROJECT REPORT FORM (Cont'd)

NC-147(c)
SERIAL NO.

(E) Significance to NCI Program. (Cont'd.)

3) Relative evaluation of the several accepted methods, (including vaginal aspiration) for recognition and diagnosis of uterine cervical cancer.

4) Source of information for comparison with existing data on incidence and prevalence of uterine cervical cancer in various segments of the female population of the United States.

5) Independent evaluation of vaginal cytology as a case finding method for uterine cervical cancer for comparison with data from other population groups in other geographical areas.

(F) Proposed Course of the Project.

A three to five year (appropiations permitting) case-finding program and clinical research evaluation of uterine cervical cancer in the adult female population of Greater Columbus, Ohio.

PROJECT REPORT FORM (Cont'd)

10. NCI-147(c)
SERIAL NO.

11. BUDGET ACTIVITY:

RESEARCH ☐ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

12. COOPERATIVE RELATIONSHIPS:

This is a joint project of the Ohio State University Medical School the Field Investigations and Demonstrations Branch with cooperation of the Columbus Academy of Medicine, the Columbus City Health Department, the Practicing physicians of Columbus and Franklin County, Ohio, and the Colum and Franklin County units of the American Cancer Society under a plan drew up cooperatively by the University and the Branch (November 29, 1955.)

13. RELATED RESEARCH:

A number of parallel investigations under NCI research grants and several parallel studies in other geographical locations being conducted cooperatively by University Groups and the Field Investigations and Demonstrations Branch.

NO ENTRIES ON ITEMS 14, 15 & 16.

PROJECT REPORT FORM

1. Cancer INSTITUTE
2. Field Investigations & Demonstrations Branch LABORATORY OR BRANCH
3. Field Studies Sections SECTION OR SERVICE
4. LOCATION (IF OTHER THAN BETHESDA)
5. NCI-148 SERIAL NO.

Possible effects of atomic fall-out as reflected in vital statistics
PROJECT TITLE

B. E. Carroll
PRINCIPAL INVESTIGATOR (S)

Dr. S. C. Ingraham, P. A. Lawrence, Dr. V. Archer
OTHER INVESTIGATORS

PROJECT DESCRIPTION

(A) Objective

To detect possible harmful effects of fall-out from nuclear weapons testing through their influence on those vital statistics which would be affected by harmful genetic changes in the population or by increased cancer incidence.

(B) Methods Employed

1) Items of vital statistics which might be affected by direct or by genetic effects of radiation from atomic fall-out will be tabulated for a base-line period of 10 years and for each year following the start of nuclear weapons testing in Nevada.

2) The items to be tabulated include sex ratio among live births, infant death rates, fetal death ratios, birth rates, death rates from congenital malformations, and death rates from cancer.

3) The tabulations will be made geographically on the basis of the approximate path of prevailing winds from the Nevada test site in the search for possible changes along this path which do not occur in other areas.

(C) Major Findings

None.

NCI-148
SERIAL NO.

PROJECT REPORT FORM (Cont'd)

(D) Significance to Cancer Research

1) Any increase in cancer mortality along the path of atomic fallout which did not occur in other areas and not otherwise explained would raise the presumption of increased cancer incidence due to radiation damage.

2) Any unexplained increase in the other items to be tabulated would raise the presumption of radiation damage to the populations concerned and of possible increases in cancer incidence some years later.

(E) Proposed Course of Project

1) Statistics for the base-line years have been partly tabulated.

2) Vital statistics for 1951-52-53 are now available, so that very preliminary results can be obtained within a few months. Conclusive results may not be forthcoming, however, for a few more years.

PROJECT REPORT FORM (Cont'd)

0. NCI-148
SERIAL NO.

1.
BUDGET ACTIVITY:

RESEARCH	/_/	ADMINISTRATION	/_/
REVIEW & APPROVAL	/_/	TECHNICAL ASSISTANCE	/X/

12.
COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 or 1957

None.

13.
IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

None.

NO ENTRIES FOR ITEMS 14, 15 & 16.

PROJECT REPORT FORM

1. Cancer — INSTITUTE
2. Field Investigations & Demonstrations Branch — LABORATORY OR BRANCH
3. Field Studies Sections — SECTION OR SERVICE
4. Boston, Massachusetts — LOCATION(IF OTHER THAN BETHESDA)
5. NCI-149 (C) — SERIAL NO.

6. Environmental Exposure and medical history, with emphasis on pregnancy-time, of mothers of leukemic children (ages 0-14 yrs.) — PROJECT TITLE

7. M. Manning — PRINCIPAL INVESTIGATOR(S)

8. R. F. Kaiser — OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

(A) Objectives

1) This study was listed in 1954 as included in NCI-116 into a "Leukemia project", a "Lymphomata" project and an "other cancer" project. This is the leukemia project.

2) To determine whether anything in the environment of the mother may have caused, contributed to or precipitated leukemia in the child (by means of transplacental transfer of a possible hypersensitivity with the bone marrow as the shock organ.)

(B) Methods Employed

1) A question sheet was developed which would include pertinent data concerning both the mother and the child.

2) Mothers of leukemic children (ages 0-14) are interviewed early in the course of the child's disease. Particular care is taken not to relate the questions to the child in such a way as to disturb the mother, and similar questions are asked about other siblings.

3) Hospital records of the mother are reviewed if they contain data pertinent to the question sheet.

4) Industrial exposures are followed up where practicable.

NCI-149 (C)
SERIAL NO.

PROJECT REPORT FORM (Cont'd)

5) Material from question sheets is collated and studied, for facto common to the several cases.

(C) Major Findings

1) Mothers of leukemic children show a higher incidence of hay feve asthma, and hives than mothers of (a) normal children and (b) Mother of children with other malignancies. If lymphoma cases are excluded from "other malignancies" the difference in incidence of allergy histories for the mothers is even more impressive.

2) Mothers of leukemic children have a history of greater industria exposure to possible carcinogens, than do mothers of the control gro of children, or do mothers of the children with other malignancies.

3) Mothers of leukemic children report in their histories a higher incidence of blood transfusions, exposure to salicylates, antihistam tonsillitis, viral diseases, miscarriage, stillbirth, exposure to pa or varnish, frequent use of bleach, and use of insect spray.

4) Mothers of leukemic children are older at marriage (Age of mothe at birth of leukemic child has not been tabulated)

5) Smoking histories are parallel in all groups of mothers questio

(D) Significance to Cancer Research

1) This study has uncovered the facts noted above which, with furth studies may help establish an etiological factor or factors in acut leukemia in child-hood.

2) This study already implies that leukemia may have a different etiology from other cancers of childhood.

3) Several avenues of approach are opened for further investigatio of prenatal and postnatal environmental influences on childhood can

(E) Proposed Course of Project

1) To continue interviews with mothers of leukemic children

2) To tabulate results for correlation of factors in common

3) To correlate the known significant factors with child's respons to (1) therapy, (2) course of the disease, and (3) blood findings

4) To develop laboratory tests which will corroborate the findings of the questionnaire.

5) To extend the studies to other hospitals in this area, and to the areas.

6) To extend studies to other age groups,

PROJECT REPORT FORM (Cont'd)

NCI-149 (C)
SERIAL NO.

BUDGET ACTIVITY:

RESEARCH	/_/	ADMINISTRATION	/_/
REVIEW & APPROVAL	/_/	TECHNICAL ASSISTANCE	/X/

COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 or 1957:

Children's Hospital, Boston, Massachusetts
Children's Cancer Research Foundation, Boston, Massachusetts
Children's Medical Center, Boston, Massachusetts

IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

None.

ENTRIES FOR ITEMS 14, 15 & 16.

PROJECT REPORT FORM

1. Cancer — INSTITUTE
2. Field Investigations & Demonstrations Branch — LABORATORY OR BRANCH
3. Field Studies Sections — SECTION OR SERVICE
4. — LOCATION (IF OTHER THAN BETHESDA)
5. NCI-150 — SERIAL NO.

6. Geographic Distribution of Cancer in the U. S.
PROJECT TITLE

7. P. A. Lawrence, H. Greenville
PRINCIPLE INVESTIGATOR(S)

8. B. E. Carroll, S. C. Ingraham
OTHER INVESTIGATORS

9 PROJECT DESCRIPTION

(A) Objectives:

To map the distribution of mortality due to malignant disease within the United States and to see if any geographic patterns exist which might be correlated with variations in known geological, topographical, or other features of the country.

(B) Methods Employed

Utilizing mortality data published by the NOVS for the years 1949, 1950 & 1951, the relative frequency of death reported to have been caused by cancer was computed for each county within the U. S. The ratios so calculated for the counties within each State were then assayed in descending order of magnitude, and split into quartiles. On a map the top 25% of the counties within each State were painted red, and the second 25% were painted yellow.

(C) Major Findings

1) The resultant map shows definite groupings of contiguous counties within states. These groupings, in many cases, differ from those patterns shown by mapping of population density.

2) In several notable instances there are patterns which extend across as many as three different state boundaries, and one striking pattern seems to follow the Appalachian mountains chain from Alabama into New England. Other notable patterns are found in Florida, Kentucky and Central Texas.

PROJECT REPORT FORM (Cont'd)

NCI-150
SERIAL NO.

(D) Significance to Cancer Research

This project constitutes a method for locating geographic areas showing apparent anomalies in the occurrence of malignant disease. As these ar are located it is proposed that they be studied individually for unusua environmental factors which might account for the anomalies.

(E) Proposed Course of the Project

The maps developed to date are based upon data which are known to be cr As time and personnel become available, more refined figures can be dev eloped and the accuracy and significance of the maps will be improved.

PROJECT REPORT FORM (CONTD)

10. NCI-150
SERIAL NO.

12. BUDGET ACTIVITY:

RESEARCH ☐ ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☒

13. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 or 1957:

None.

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR Funds), IDENTIFY SUCH RESEARCH

None

N ENTRIES FOR ITEMS 14, 15 & 16.

PROJECT REPORT FORM

1. Cancer — INSTITUTE
2. Field Investigations & Demonstrations Branch — LABORATORY OR BRANCH
3. Field Studies Sections — SECTION OR SERVICE
4. Berkeley, California — LOCATION (IF OTHER THAN BETHESDA)
5. NCI-151(c) — SERIAL NO.

6. Cervical Smear Cytology as a means of cancer Case Finding--San Diego, Calif. — PROJECT TITLE

7. John E. Dunn, Jr., M. D. — PRINCIPAL INVESTIGATOR(S)

8. Dr. Purvis Martin and Collaborators — OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

(A) Objectives

1) To extend the activities of the cytology work of the Gynot Clinic to include indigent women of San Diego City and County.

2) To make available data on this segment of the population regarding cervical cancer for study along with the data already available from examinations of some 40,000 private patients.

(B) Methods Employed

1) The Gynot Clinic is composed of a group of gynecologists, operating a cytology laboratory jointly, who are thoroughly convinced of the value of cervical cytology in cervical cancer case finding. They have operated their laboratory at minimum fees to make the service as widely available as possible to other physicians as well as their own group. They have not been able to extend their service to indigent women.

2) The cytology laboratory has excellent professional and technical supervisory personnel and extension of the case finding program to the

PROJECT REPORT FORM (Cont'd)

NCI-151(c)
SERIAL NO.

Methods Employed (Cont'd)
indigent population can be accomplished through the addition of screen technicians. Two such technicians will be added for this purpose.

(C) Major Findings.

1) None as yet since the project is only starting. The Gynot Clinic is beginning an analysis of their accumulated data to date with a special Projects Grant awarded for that purpose.

(D) Significance to Cancer Research

1) The study will provide data on the findings from screening patient using direct cervical specimens. (Memphis is using vaginal pool specim

2) From the standpoint of cancer control, it will be of interest to l whether private physicians can effectively promote a program of commun case finding.

(E) Proposed Course

To extend the activities of the cytology work of the Gynot Clinic to indigent women and to analyze accumulated data.

(F) Patient Material

Both private and indigent female patients who are seen in a selected gynecology clinic in a California city. Private physicians in the ar also send slides to the laboratory.

PROJECT REPORT FORM (Cont'd)

NCI-151(c)
SERIAL NO.

BUDGET ACTIVITY:

RESEARCH	☐	ADMINISTRATION	☐
REVIEW & APPROVAL	☐	TECHNICAL ASSISTANCE	☒

COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 or 1957:

Gynot Clinic, San Diego, California

IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

A number of parallel investigations under NCI research grants and several parallel studies in other geographical locations being conducted cooperatively by University Groups and the Field Investigations and Demonstrations Branch.

PROJECT REPORT FORM (Cont'd)

14. NCI-151(c)
SERIAL NO.

15. PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1955:

Dunn, John E., Jr. Screening for Cancer, J. Chronic Diseases 2 : 450-460 (Oct.) 1955.

Dunn, John E. Jr., and Sprunt, D. H., Uterine Cancer Case-Finding by Vaginal Cytology. Public Health Reports 70: 341-346 (April) 1955.

16. None

HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1955.

PROJECT REPORT FORM

1. Cancer — INSTITUTE
2. Field Investigations & Demonstrations Branch — LABORATORY OR BRANCH
3. Field Studies Sections — SECTION OR SERVICE
4. Framingham, Massachusetts — LOCATION(IF OTHER THAN BETHESDA)
5. NCI-152(C) — SERIAL NO.
6. Correlation of Thyroid Disease and Breast Cancer — PROJECT TITLE
7. John Vander, M.D. — PRINCIPAL INVESTIGATOR(S)
8. W. S. Baum, M. D.; R. F. Kaiser — OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

(A) Objective

To determine if there is a relationship between carcinoma of the breast and thyroid disease.

(B) Methods Employed

In a very large thyroid clinic to determine the incidence of breast carcinoma among the thyroid patients with especial emphasis on those with myxedema.

(C) Major Findings.

None. The project was initiated late in 1955.

(D) Significance to Cancer Research

A number of observers hold the clinical impression that cancer of the breast is frequently associated with thyroid disease. This seems to be particularly true of patients with non-toxic thyroid nodules and spontaneous myxedema. If a relationship between thyroid disease and carcinoma of the breast is indeed shown to exist it would throw more light on the relationship between hormones and cancer.

NCI-152(C)
SERIAL NO.

PROJECT REPORT FORM (Cont'd)

(E) Proposed Course of Project

A study of patients and records in a large thyroid clinic in which the principal investigator is doing clinical work. This clinic has been in existence for over 35 years and has a very excellent, prolonged follow-up system possibly unsurpassed by any other. The records are also excellent both as relates to thyroid disease as well as other illnesses. There is a close working relationship between the thyroid clinic and the breast cancer clinic in the same institution. If the suspected relationship is verified, a more basic study on endocrines and cancer (with preliminary emphasis on TSH) may be indicated.

(F) Patient Material

Patients seen in a large thyroid clinic in a New England city.

PROJECT REPORT FORM (Cont'd)

10 NCI-152(C)
SERIAL NO.

11 BUDGET ACTIVITY:

RESEARCH	[ ]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	TECHNICAL ASSISTANCE	[X]

1. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 or 1957:

None.

). IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

None.

O ENTRIES FOR ITEMS 14, 15 & 16.

PROJECT REPORT FORM

1. Cancer INSTITUTE
2. Field Investigations & Demonstrations Branch LABORATORY OR BRANCH
3. Field Studies Sections SECTION OR SERVICE
4. Washington, D. C. LOCATION(IF OTHER THAN BETHESDA)
5. NCI-153(C) SERIAL NO.
6. Vaginal Cytology as a case-finding method in uterine cancer (American Indians) PROJECT TITLE
7. Paul Ortega, Mrs. Weir PRINCIPAL INVESTIGATOR(S)
8. Samuel C. Ingraham, II, Raymond F. Kaiser OTHER INVESTIGATORS
9. PROJECT DESCRIPTION

(A) Objectives

1) Investigation of the usefulness of vaginal aspiration as a test for uterine cancer in a selected American Indian Population

2) Correlation of tissue studies with results of exfoliative cytology on the above population

3) Comparison of uterine cervical cancer and its occurrence rate among American Indians with similar information from other population groups

(B) Methods Employed

1) In cooperation with the Indian Health Service, Bureau of Medical Services, a vaginal smear is obtained on all adult females participating. This smear after fixation is air-dried and mailed to the Washington, D.C. cytology laboratory.

2) All smears are screened and checked by technicians with pathologists making the final diagnosis.

3) Suspicious cases are to be followed by the nearest hospital facility where indicated smear or tissue studies are carried out.

4) All tissue removed will be sent to the Washington, D. C. laboratory for processing and diagnosis, and definitive therapy accordingly determined.

NCI-153(c)
SERIAL NO.

PROJECT REPORT FORM (Cont'd)

5) All cases will have an adequate personal history available for purposes of follow-up, and correlation with the laboratory results.

6) All clinical, cytological and histological results obtained from this study will be coded and placed on IBM punch cards for analysis.

7) This material after analysis will then be compared to results obtainable from other population surveys in other racial groups.

(C) Patient Material

1) The source material for the smears is a group of American Indian females so selected as to represent a significant sample of several Reservation populations.

(D) Major Findings

None. This program was initiated November 1955 and some smear screening has just begun.

(E) Significance to National Cancer Institute

This study represents a unique opportunity to apply cancer testing techniques previously demonstrated as adequate to a new ethnic group previously untested. Scattered personal experience indicates the presence of uterine cancer among the American Indian, but its true incidence and prevalence is unknown. This pilot study will afford suggestive evidence as to the desirability of expanding cancer testing to a wider segment of the Indian population.

(F) Proposed Course of Project

Over a period of six months or more material will be collected from various reservations and the results tabulated. When the volume of data collected is believed adequate, this project will be reviewed and a decision reached regarding continuation or possible expansion of this project.

PROJECT REPORT FORM (Cont'd)

10. NCI-153 (C)
SERIAL NO.

11. BUDGET ACTIVITY:

RESEARCH	[ ]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	TECHNICAL ASSISTANCE	[X]

12. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 or 1957

Indian Health Service, BMS, Public Health Service

13. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

A number of parallel investigations under NCI research grants and several parallel studies in other geographical locations are being conducted cooperatively by University Groups and the Field Investigations and Demonstrations Branch.

0 ENTRIES FOR ITEMS 14, 15 & 16.

[illegible]

PROJECT REPORT FORM

1. Cancer 2. Field Investigations & Demonstrations Branch

3. Field Studies Sections 4. Washington, D. C. 5. NCI-154-c-
SECTION OR SERVICE LOCATION (IF OTHER THAN BETHESDA) SERIAL NO.

6. Vaginal cytology as a case-finding method in uterine cancer, Washington, D. C.
PROJECT TITLE

7. Paul Ortega
PRINCIPAL INVESTIGATOR(S)

8. Samuel C. Ingraham, II, Raymond F. Kaiser
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

(A) Objectives

1) Investigation of usefulness of vaginal aspiration as a test for uterine cancer in the adult female population of Washington, D. C.

2) Correlation of tissue studies with results of exfoliative cytology on the above populations.

3) Comparison of uterine cervical cancer and its occurrence rate in Washington, D. C. with similar information from other geographic areas.

(B) Methods Employed

1) Using the customary Papanicolaou technique, vaginal smears and where indicated cervical smears are obtained and stained. All smears are screened and checked by technicians with pathologists making the final diagnosis.

2) Suspicious cases will have tissue studies as indicated and medically accepted. Tissue removed will be reviewed and correlated with the respective smear.

3) Confirmed cases will be referred to proper medical agencies for definitive therapy, and any pathological specimens thereby resulting will be reviewed.

4) All cases will have a medical history and enough personal information obtained to insure adequate follow-up and evaluation of the method itself as a testing device.

PROJECT REPORT FORM (Cont'd)

CI-154-(c)
SERIAL NO.

Methods Employed (Cont'd)

5) All cytological and histological results as well as pertinent clinic data will be coded and placed on IBM punch cards and this material will collated, correlated and analyzed.

(C) Patient Material

1) Adult female employees of HEW in Washington, D. C.

2) Rescreening of adult female employees of NIH, Bethesda

3) Other selected groups of female adults in the Washington, D. C. area

(D) Major Findings

None. Program organization was initiated November 1955. It is anticipated that patient screening should be started by March 1956.

(E) Significance to National Cancer Institute

Further information will become available regarding the demography of human cervical carcinoma and pre-cancerous states. Moreover this will represent not only repetition of previous methods but provide an opportunity to acquire new basic information regarding this group of diseases.

(F) Proposed Course of Project

A three to five year investigative and case-finding program is contemplated.

PROJECT REPORT FORM (Cont'd)

10. NCI-154(c)
SERIAL NO.

11. BUDGET ACTIVITY:

RESEARCH		ADMINISTRATION	☐
REVIEW & APPROVAL	☐	TECHNICAL ASSISTANCE	☒

12. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 or 1957:

None.

13. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

A number of parallel investigations under NCI research grants and several parallel studies in other geographical locations are being conducted cooperatively by University Groups and the Field Investigations and Demonstrations Branch.

N ENTRIES FOR ITEMS 14, 15 & 16.

PROJECT REPORT FORM

1. Cancer — INSTITUTE
2. Field Investigations & Demonstrations Branch — LABORATORY OR BRANCH
3. Field Studies Sections — SECTION OR SERVICE
4. — LOCATION(IF OTHER THAN BETHESDA)
5. NCI-155 — SERIAL NO.
6. Monthly and Quarterly Reports — PROJECT TITLE
7. Miriam Barnes — PRINCIPAL INVESTIGATOR(S)
8. Pope A. Lawrence, Samuel C. Ingraham, Benjamin Carroll — OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

(A) Objectives

1) To provide for the Chief, Field Investigations and Demonstrations Branch, the Chief, National Cancer Institute regular, periodic summaries of the individual field project operations and of the total activities of the Field Studies Sections.

2) To help keep the Heads of the Field Studies Sections currently informed of progress in the individual field projects and of activities of the several Field Investigators,

3) To have on hand current summaries of total program operations of the Field Studies Sections in order to have accurate information available for answering inquiries and for program planning,

(B) Methods Employed

It is a direct job assignment of the principal investigator to obtain monthly reports of field operations from the Field Investigators. From these, plus information from interoffice memoranda, letters, telephone conversations, trip reports, special reports, instructions from the Section Heads, conversations with visiting Field Investigators and other sources the Investigator abstracts pertinent information, compiles it sequentially and composes monthly and quarterly reports of the Section program activities.

NCI-155
SERIAL NO.

PROJECT REPORT FORM (Cont'd)

(C) Major Findings

1) Twelve(12) annual reports and four quarterly reports were prepare

2) Data from the monthly and quarterly reports plus special ad hoc reports from the Field Investigators are used in preparing the Annual Project Reports.

(D) Significance to National Cancer Institute Program

Within the Field Studies Sections, the monthly and quarterly reports e an important factor in assaying work of the Field Investigators, progress the individual projects and planning of program activities for future proj ts.

The monthly and quarterly reports also keep the Chief, Field Investig tions and Demonstrations Branch currently informed of Field Studies Sectio activities.

(E) Proposed Course of the Project

The monthly and quarterly reports of the Field Studies Sections is a continuing activity.

PROJECT REPORT FORM (Cont'd)

0. NCI-155
SERIAL NO.

1.

BUDGET ACTIVITY:

RESEARCH	/_/	ADMINISTRATION	/_/
REVIEW & APPROVAL	/_/	TECHNICAL ASSISTANCE	/X/

2.

COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 or 1957:

None.

IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

None.

ENTRIES FOR ITEMS 14, 15 & 16.

PROJECT REPORT FORM

3. National Cancer Institute — INSTITUTE
2. Field Investigations & Demonstrations Branch — LABORATORY OR BRANCH

4. Field Studies Section — SECTION OR SERVICE
4. Madison, Wisconsin — LOCATION (IF OTHER THAN BETHESDA)
5. 156 — SERIAL NO.

6. Study of Cytology as a Means of Uncovering Cervical Cancer on a Mass Basis — PROJECT TITLE

7. Dr. William D. Stovall and R. F. Kaiser, M.D. — PRINCIPAL INVESTIGATOR(S)

8. Dr. Samuel C. Ingraham, II — OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

A. OBJECTIVES

This study is designed to explore the feasibility and practicability of bringing the cytologic procedure to rural women in a six-county area, utilizing physicians to gather the necessary specimens and submit them to a central laboratory for interpretation. The study will provide data for comparison of vaginal aspiration and cervical scraping smears. In addition, the study will provide data on the prevalence and incidence of carcinoma-in-situ and invasive cervical cancer in a rural population of approximately 350,000 women.

B. METHODS EMPLOYED

Through a cooperative arrangement between the University of Wisconsin Medical Center and the Branch a project is being established which will provide study material and laboratory interpretation of vaginal and cervical smears. The study will be under the direction of Dr. William D. Stovall of the University of Wisconsin with technical, administrative and professional staff being provided by the National Cancer Institute. Laboratory space and its maintenance will be provided by the University. Supplies and equipment necessary to the study are being supplied by NCI.

The project was in its organizational and developmental stage during the latter months of 1955, consequently there are no findings to report. Staffing will be completed in the future and it is anticipated the project will be in full operation during the spring of 1956 and will extend over 3 to 5 years.

10. 156
SERIAL NO.

11.
BUDGET ACTIVITIES:

RESEARCH [ ] ADMINISTRATION [ ]
REVIEW & APPROVAL [ ] TECHNICAL ASSISTANCE [X]

12. University of Wisconsin Medical Center, Laboratory of Hygiene
COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 OR 1957

13. Other parallel cooperative investigations are being established in four other areas.
IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS) IDENTIFY SUCH RESEARCH:

NO ENTRIES FOR ITEMS 14, 15, AND 16

1. National Cancer Institute — INSTITUTE
2. Field Investigations and Demonstrations Branch — LABORATORY OR BRANCH
3. Grants Section — SECTION OR SERVICE
4. Louisville and Jefferson County Kentucky — LOCATION (IF OTHER THAN BETHESDA)
5. 157 — SERIAL NO.

6. Study of vaginal and cervical exfoliative cytology as a method of finding cervical and uterine cancer — PROJECT TITLE

7. James C. Drye and Noka B. Hon, M.D. — PRINCIPAL INVESTIGATOR(S)

8. William M.Christopherson — OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

A. OBJECTIVES

The study is designed (1) to provide comparative cervical and uterine incidence and prevalence data on a major population group with special reference to racial and economic status, (2) to provide data on the 15-20 age group which is not now available, (3) to correlate tissue studies with results of the exfoliative cytology findings on this population, (4) to determine how an exfoliative cytology laboratory can become a self-supporting community medical diagnostic service, (5) to give special consideration to a cost study as applied to a community screening program.

B. METHODS EMPLOYED

Under the direction of the Department of Pathology, University of Louisville Medical School and the Tumor Board, Medical Center, University of Louisville, vaginal and cervical smears will be obtained by various methods, prepared and examined according to the usual Papanicolaou technique on the adult female population. All smears will be screened and checked by technicians with a pathologist reviewing all suspicious slides and making the final diagnoses. All suspicious or positive cases will have tissue studies. Suspicious cases will be followed regularly. The cases found to be positive by biopsy will be treated or referred for treatment.

19. Serial No. 157

Statistical procedure:

(a) History card designed by National Cancer Institute will be completed on each patient smeared.

(b) Recall of all patients who are questionable - repeat or biopsy.

(c) Recall at one year of all those smeared.

(d) Transfer of all data to punch cards for tabulation.

(e) Report to be prepared annually and will contain customary data for this type study.

Population - There are 200,000 women over 20 years of age. About 13% are non-white.

C. MAJOR FINDINGS

This program was initiated September 1, 1955 and officially received the endorsement of J. Murray Kinsman, Dean of School of Medicine on September 2, 1955. Subsequently, all organized medical groups in the State, county and city concerned with this type of activity have given official approval of the study. Cooperating groups sponsoring the program are State Division of the American Cancer Society and the Kentucky State Department of Health.

The building to house the project has been secured and reconditioning and alteration of the building will be completed within the next two months. Four persons have been recruited for cytology training and at present are in training at Memphis, Tennesse. Actual screening of slides will start April 1, 1956 when the screener return from training. Two clerks are now employed and are being trained in the record system to be used in the study.

D. SIGNIFICANCE TO NATIONAL CANCER INSTITUTE

The results of this study will add to the information being obtained in other cytological studies which is necessary to establish statistically significant facts in cytology before it can be recommended for mass use as a cancer screening method. It will provide a means of professional education in the use and reliability of cytology in the general practice of medicine.

E. PROPOSED COURSE OF PROJECT

The study is organized to continue 3 to 5 years with the ultimate aim of becoming a permanent community supported diagnostic service.

10. 157
SERIAL NO.

11.
BUDGET ACTIVITY:

RESEARCH	☐	ADMINISTRATION	☐
REVIEW & APPROVAL	☐	TECHNICAL ASSISTANCE	☒

12.
COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 or 1957

University of Louisville School of Medicine, State Division of American Cancer Society, Kentucky State Department of Health.

NO ENTRIES FOR ITEMS 13, 14, 15, 16

PROJECT REPORT FORM

1. National Cancer Institute — 2. Field Investigations & Demonstrations Br.
INSTITUTE — LABORATORY OR BRANCH

3. Nursing — 4. T-6 — 5. NCI 158
SECTION OR SERVICE — LOCATION (IF OTHER THAN BETHESDA) — SERIAL NO.

6. Use of Consultant Service in Planning Nursing Programs
PROJECT TITLE

7. F. Ruth Kahl
PRINCIPAL INVESTIGATOR(S)

8.
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

A. Objective to increase interest and knowledge regarding cancer among industrial nurses in order that they will be alert to detect employees showing signs or symptoms of cancer and refer them for medical care.

B. Method - Educational programs for industrial nurses. The problem is how to reach and interest industrial nurses in such educationa, programs -- what is a practical period and spacing of time for them. A State and the Federal Nursing Consultant in Occupational Health were called in to explore the problem with Nursing Section F.I.D.B.-N.C.I. (2 days conference).

C. Activities Suggested:

a. that the possibilities for inclusion of cancer in the on-going Industrial Health educational programs in the University of Minnesota and in Yale University be explored. These programs are planned with the respective industrial nursing organizations in accordance with their felt needs. Cancer might be the vehicle for study of methods to change emphasis in their plant programs from emergency care to health maintenance.

b. Workshops on a regional basis for State Occupational Health personnel with consultants in other chronic disease areas (in addition to cancer) for the purpose of developing working plans for interesting industrial nurses in both early case finding and in rehabilitation of employees with cancer or any of the "chronic diseases".

c. Significance of project: industry provides the daily assembly of large numbers of employees each of whom is a potential candidate for any one of these diseases. Industrial nurses have won their confidence -- they see their employees daily and consequently they should be able to detect early signs of symptoms and encourage the individuals to seek medical care without delay.

PROJECT REPORT FORM (Cont'd)

10. NCI 158
SERIAL NO.

11.
BUDGET ACTIVITY:

RESEARCH [X] ADMINISTRATION [ ]

REVIEW & APPROVAL [ ] TECHNICAL ASSISTANCE [X]

12.
COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 or 1957

Cooperative relationships -- the interest and cooperation of State Department and Industrial Insurance Carrier Consultants as well as of industrial management and the industrial physicians and nurses must be secured if this unparalleled opportunity for case finding is to be utilized.

13.
IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

No entries for items 14, 15, and 16.

PROJECT REPORT FORM

1. National Cancer Institute — INSTITUTE
2. Field Investigations and Demonstrations Br. — LABORATORY OR BRANCH
3. Nursing — SECTION OR SERVICE
4. T-6 — LOCATION (IF OTHER THAN BETHESDA)
5. NCI 159 — SERIAL NO.

6. Vaginal Cytology Testing of Female Employees at N.I.H. — PROJECT TITLE

7. Mary Bouser — PRINCIPAL INVESTIGATOR(S)

8. Dr. William Baum, Dr. John Lynch, Mrs. Frances Wolford — OTHER INVESTIGATORS

9. PROJECT D$SCRIPTION

a. Objectives

1. To determine participation and interest of female employees in taking advantage of the opportunity for detection of early or pre-invasive cancer of the cervix.

2. To interest the health facility of the Institutes in adopting the vaginal cytology screening test for cancer as a part of their regular physical examination.

3. To offer a proven cancer detection service to the eligible population.

4. To develop methods whereby this test could be offered to other groups of women.

b. Methods Employed

1. Preliminary planning with related units.

a. Employees Health Service

b. Surgical and Medical Service of N.C.I.

c. Pathology Department of University of Tennessee (reading of slides)

2. Obtaining administrative clearance

a. For conducting the program

b. For contacting female employees

3. Explanatory talk to women employees

PROJECT REPORT FORM (Cont'd)

4. Collection of specimens - 1311 individuals tested from March 28 through September 1. Material obtained by vaginal pipetting of fluid from posterior fornix, placed on slide and fixed in 50% solution of ether and 95% alcohol. Slides were mailed to Memphis for reading and interpretation.

c. Patient Material

1. Listing of female employees obtained from Statistical Processing Section - approximately 1800 women.

2. Participating women - 1311

d. Major Findings

1. Positive findings determined through biopsy after detection by cytology - 4.

2. Suspicious findings unconfirmed by biopsy - 7.

3. Percent participation - based on average of 1800 employees - 72.8

4. Interest demonstrated by Employees Health Service - Cytology incorporated as part of pre-employment examination done on women the Health Unit.

e. Significance to the Program of the Institute

1. Demonstrated interest of women in having the test.

2. Demonstrated interest of personnal of Health Service and willingne to incorporate this testing into their program.

3. Demonstrated simplicity of taking smears and adaptability of this program to existing Health Service programs.

4. Served as pilot study and a basis for consultative service in a vaginal cytology testing program.

f. Proposed Course of Project

1. To be continued by Employees Health Service

a. As part of pre-employment examination.

b. As annual screening service to female employees of N.I.H.

2. Consultant service and auxiliary assistance to be offered by N.C.I to employees Health Service, HEW, and other agencies both official nd unofficial.

PROJECT REPORT FORM (Con'd)

3. Laboratory Service

a. - Slides from pre-employment examinations to be read at N.I.H.

b. Slides in large numbers from annual screening to be read through services of N.C.I.

PROJECT REPORT FORM (Cont'd)

10. NCI 159
SERIAL NO.

11.
BUDGET ACTIVITY:

RESEARCH ☐ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE [X]

12.
COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 or 1957

a. Employees Health Service

b. Memphis - Shelby County Project

c. Medical and surgical services of N.C.I. at Clinical Center

13.
IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

Participation and Cooperation

a. Memphis - Shelby County Vaginal Cytology testing program

1. Reading and interpretation of slides

2. Assistance in planning and orientation to program in pre-planning stage

b. Employees Health Service

1. Provision of space and physical facilities

2. Assistance with interpretation of findings

3. Assistance with follow-up

c. Medical and Surgical Service - N.C.I. - Clinical Center. Follow-up and diagnostic assistance

d. Pathology Department - Clinical Center - Reading and interpretation of cervical smears and biopsies.

No entries for items 14, 15, and 16.

PROJECT REPORT FORM

1. National Cancer Institute — INSTITUTE
2. Field Investigations and Demonstrations-Br. — LABORATORY OR BRANCH
3. Nursing Section — SECTION OR SERVICE
4. T-6 — LOCATION (IF OTHER THAN BETHESDA)
5. NCI 160 — SERIAL NO.

6. Work Conference on Evaluation Tools — PROJECT TITLE

7. Rosalie I. Peterson, Margaret Knapp — PRINCIPAL INVESTIGATORS

8. Dr. Louis Heil (Consultant) — OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

(1) Objective

To develop instruments for the evaluation of cancer nursing in the basic professional curriculum.

(2) Methods Employed

Cancer Nursing Consultants from the five university schools of nursing, recipients of cancer special grants and the consultant, a specialist in the field of evaluation and educational research, worked together with the nursing staff to refine and develop tools of evaluation designed to (a) measure nurse patient relationships in the care of cancer patients, (b) measure the nurse's problem-solving ability, (c) refine the cancer knowledge test for nurses.

(3) Major Outcomes:

a. Underlying principles to be used for measurement were determined

b. Changes in scripts were made

c. Schedules for testing nurse patient relationship in student groups in the five grantee schools and control schools were decided upon and testers assigned.

d. Options to be tested for validity and reliability for the knowledge test were selected.

(4) Significance to Nursing Section - F.I.D.B.

The tools developed in the work conference on evaluation tools will aid in determining student nurse attitudes, nursing skills and cancer knowledge. When these are sufficiently refined, they can be used generally

in the field of nursing. It is felt that knowledge in cancer will increase among faculty members, nursing service personnel and students where the tests are administered. This should reflect in earlier case finding, large survival groups and greater rehabilitation of patients.

(5) Proposed Course of Project

a. Refinement of present tools after re-testing in project schools and control groups. The tools of evaluation of nurse patient relationships will then be ready for distribution to other schools.

b. Giving the cancer knowledge test for the second time to the same selected 95 schools of nursing.

c. Conducting further work conferences to develop tools of evaluation in the area of problem-solving.

PROJECT REPORT FORM (Cont'd)

10 NCI 160
SERIAL NO.

11

BUDGET ACTIVITY:

RESEARCH ☐ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE [X]

12

COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 or 1957
Cooperative Relationships
The five grantee schools, Skidmore College, N. Y., Boston University, Boston, Vanderbilt "U", Nashville, Tenn., Washington "U", St. Louis, "U" of Calif., Los Angeles.

Approximately 100 schools of nursing throughout the country.

1.

IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

The five grantee schools mentioned above are all attempting to integrate cancer nursing in the Basic Professional Curriculum. The cancer nursing project directors in all five schools are using the cancer nursing monograph prepared by the Nursing Section of F.I.D.B. for content material.

No entries for Items 14, 15, and 16.

PROJECT REPORT FORM

1. National Cancer Institute — INSTITUTE
2. Field Investigations and Demonstrations Branch — LABORATORY OR BRANCH

3. Nursing Section — SECTION OR SERVICE
4. T-6 — LOCATION (IF OTHER THAN BETHESDA)
5. NCI-161 — SERIAL NO.

6. Cancer Nursing Bibliography — PROJECT TITLE

7. Margaret F. Knapp — PRINCIPAL INVESTIGATOR

8. Rosalie I. Peterson, F. Ruth Kahl, Mary Bouser — OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Annotated bibliography on articles, books, bulletins, films and other visual aids.

(1) Objectives: The objective of this project is to compile an annotated bibliography on printed materials and visual aids for nursing educators in basic and advanced nursing programs.

(2) Methods Employed: The bibliography is a compilation of information entered on individual filing cards.

(3) Significance to Cancer Nursing: Provides references which will enable nursing instructors to improve their cancer nursing instruction.

(4) Proposed course of project: The bibliography is distributed to the 1200 nursing schools in the country and to all universities offering advanced nursing programs, and to indiviual nursing educators and administrators upon request.

A new bibliography was prepared this year. This will be revised and expanded biennially.

PROJECT REPORT FORM (Cont'd)

10. NCI 161
SERIAL NO.

11.
BUDGET ACTIVITY:

RESEARCH [/] ADMINISTRATION [ ]

REVIEW & APPROVAL [ ] TECHNICAL ASSISTANCE [X]

12.
COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATION PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 195 or 1957

13.
IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

No entries for items 14, 15, and 16.

PROJECT REPORT FORM

1. National Cancer Institute — INSTITUTE
2. Field Investigations & Demonstrations Branch — LABORATORY OR BRANCH
3. Administrative Services — SECTION OR SERVICE
4. - -
5. NCI-162 — SERIAL NO.

6. Variety of administrative management functions in connection with operation of the Branch. — PROJECT TITLE

7. Dorothy G. Mathews — PRINCIPAL INVESTIGATOR(S)

8. Dr. Raymond F. Kaiser and Leona Falkowski — OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

A. Objectives:

To formulate and be responsible for the fulfillment of specialized administrative service as they apply to the operation of the several sections of the Branch -- Office of the Chief, Environmental Field Studies, General Field Studies, Grants, Nursing, and Cytology Sections.

B. Methods employed:

Participates and takes action on administrative requests of all types emanating from sections of the Branch, working out plans for the expansion and modification of medical field studies, such as recruitment, writing and reviewing job descriptions, reassignment and promotion of personnel, obtaining supplies and equipment, adjustment of space and facilities, supplying information and advice, and related matters.

Assists in the detailed administrative direction of the cytology study centers being established in widely separated areas of the country, as well as the continuing proper administrative functioning of the Cancer Investigation Unit at Memphis, Tennessee.

Provides advice and instruction to secretaries and other personnel of the Branch, both central and field units, in the proper methods of dealing with administrative matters such as preparation of requisitions, initiation of personnel actions, preparation of correspondence, travel requests, etc., which necessitates occasional travel to the field units.

Maintains records for allotment balances, transfer and disposition of property.

Participates in the formulation and compilation of special and periodic reports and directives.

10. NCI-162
SERIAL NO.

11.
BUDGET ACTIVITY:

RESEARCH [ ] ADMINISTRATION [X]
REVIEW & APPROVAL [ ] TECHNICIAL ASSISTANCE [X]

12.
COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 or 1957:

None

13.
IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

None

NO ENTRIES FOR ITEMS 14, 15 & 16.

PROJECT REPORT FORM

1. Cancer INSTITUTE
2. Field Investigations & Demonstrations Branch and Division of Special Health Services LABORATORY OR BRANCH
3. Field Studies Sections SECTION OR SERVICE
4. Salt Lake City, Utah LOCATION (IF OTHER THAN BETHESDA)
5. NCI-163 SERIAL NO.

6. Study of the cancer experience of Non-Uranium hard rock miners in the Rocky Mountain area. PROJECT TITLE

7. Miss Marian Erjavec, Dr. J. W. Egan, and P. A. Lawrence PRINCIPAL INVESTIGATOR(S)

8. Benjamin Carroll OTHER INVESTIGATORS

9 PROJECT DESCRIPTION

(A) Objectives

1) To evaluate the prevalence of cancer of the lung among underground non-uranium miners in the Rocky Mountain area.

2) To determine if a correlation exists between the levels of radon in non-uranium mines and the occurrence of lung cancer, and other causes of death.

(B) Methods Employed

1) Assembly of occupational, medical and vital statistics information on a composite group of hard-rock miners with at least 15 years of underground working experience in non-uranium mines in the Rocky Mountain States.

2) Collation and medical statistical analysis of the collected data with particular emphasis on lung cancer cases and deaths that may be discovered.

3) Collection of environmental data with respect to underground radon concentrations in the selected non-uranium mines (is being done by the Occupational Health Program Field Station in Salt Lake City in cooperation with the State Health Departments of Colorado, Utah and New Mexico).

PROJECT REPORT FORM (CONT'D)

NCI-163
SERIAL NO.

(C) Major Findings.

1) It has been established that radon concentration in the air of many of the hard-rock mines in the Rocky Mountain area appreciably exceed the Maximum Permissible Concentration as recommended by the National Committee on Radiation Protection.

2) Cooperation of several of the large hard-rock mining companies has been obtained and work was begun abstracting data from company personnel records. During 1955, approximately 60,000 records were reviewed and a list of 1,888 workers obtained who had completed 15 years of underground experience some time between 1937 and 1948. Of these, 692 are known to be dead, and the date and place of death has been recorded in almost every instance.

(D) Significance to Cancer Research

1) Data on human beings exposed to a potentially carcinogenic, radioactive environment will be compiled and so become available for possible use in cancer control. At present, such information is extremely scarce. Limited studies of mining communities in Europe have revealed high incidence of lung cancer in miners working in mines containing radioactive dust and gas. Extensive animal experiments in Europe and the Americas as well as observations made on human beings inadvertantly exposed to excessive radiation over prolonged periods of time have established beyond doubt that ionizing radiation causes cancers in animals and in people.

2) In addition, this study may yield not only information regarding levels of radiation which are harmful but also levels of radiation which miners may work and suffer no harmful effects. This information would be of value in establishing recommendations for the uranium mining industry.

(E) Proposed Course of Project

1) Review of personnel records as now being carried out will be continued until completed.

2) When all the 74,000 records have been reviewed, death records of the deceased miners will be examined. Mortality statistics will be compiled, and these data correlated with the underground mining experience records.

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PROJECT REPORT FORM (CONT'D)

3) Consideration will be given to a control study in the potash mines of New Mexico.

4) Measurement of environmental factors within the mines will be carried out by the occupational health program of the Division of Special Health Services.

5) Program will be developed for following the surviving group for mortality and causes and also for major morbidity.

PROJECT REPORT FORM (CONT'D)

10. NCI-163
SERIAL NO.

11.
BUDGET ACTIVITY:

RESEARCH [ ] ADMINISTRATION [ ]
REVIEW & APPROVAL [ ] TECHNICAL ASSISTANCE [X]

12.
COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 or 1956:

Occupational Health Field Station, Salt Lake City, Utah
State Health Departments of Colorado, Utah and New Mexico.

13.
IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS) IDENTIFY SUCH RESEARCH:

None

NO ENTRIES FOR ITEMS 14, 15 & 16.

PROJECT REPORT FORM

1. National Cancer Institute — INSTITUTE
2. Research Grants & Fellowships Branch — LABORATORY OR BRANCH
3. — SECTION OR SERVICE
4. — LOCATION (IF OTHER THAN BETH.)
5. NCI-025 — SERIAL NO.

6. Administration of cancer research grants program. — PROJECT TITLE

7. Dr. R. G. Meader — PRINCIPAL INVESTIGATOR(S)

8. Drs. C. D. Larsen, C. C. Powell, H. F. Seversmith, A. Weissler — OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: To encourage, promote, and support basic and applied research in non-Federal institutions leading toward delineation of the causes, nature, and methods of diagnosis, therapy and prevention of cancer.

Methods:

A. Preparation of awards in the name of the Surgeon General of grants for research in fields pertinent to the problem of neoplastic growth, upon recommendation of the National Advisory Cancer Council.

B. Conduct of surveys and analyses of the field of cancer research and of the research supported through cancer research grants to evaluate the extent to which all promising leads are being explored and to indicate areas in which current efforts might profitably be expanded or new efforts be initiated.

C. Exploration of new methods and techniques of administration by which the objectives might be more fully accomplished.

D. Consultation with investigators to acquaint them with the opportunities for support of expansion of their current research efforts and of development of new approaches; also to inform them of related or pertinent studies by others so their work can progress more rapidly through rapid exchange of information or through collaboration; also to aid them in administrative problems related to their research grants.

9. PROJECT DESCRIPTION (Continued)

E. Dissemination of information on research in fields related to cancer by means of conferences, symposia, publication of monographs, bibliographies, etc.

F. Provision to the National Advisory Cancer Council of special information on research grant applicants, their research problems, methods, facilities, and related research by others for the purpose of facilitating competent and adequate review of applications; accomplishment of this through correspondence, visits by staff, Council members and others, including members or representatives of Study Sections.

G. Presentation to the National Advisory Cancer Council of the technical evaluations and recommendations regarding research proposals for grants as made by appropriate Study Sections, or by special reviewers of research grant applications in those instances in which there is no existing Study Section competent to render this advice.

H. Maintenance of liaison and cooperation with the Division of Research Grants, National Institutes of Health, in the activities of the Study Sections in review of applications and with the Division of Research Grants and other Institutes of the National Institutes of Health in the development of policies and procedures for the administration of the total research grants program of the National Institutes of Health.

I. Maintenance of liaison and exchange of information with other governmental and non-governmental agencies in this country and abroad with like interests, responsibilities, and programs in order to promote collaborative efforts and to avoid unnecessary and undesirable duplication of effort. Organizations of this type include the National Science Foundation, American Cancer Society, Atomic Energy Commission, Office of Naval Research, Department of Defense, Department of Agriculture, Smithsonian Institution, Damon Runyon Memorial Fund, Jane Coffin Childs Memorial Fund, Anna Fuller Fund, British Empire Cancer Campaign, National Academy of Sciences and National Research Council, Rockefeller Foundation, International Union Against Cancer, American Medical Association, and numerous others.

J. Preparation of special and regular reports for the information of the National Advisory Cancer Council, the Director of the National Cancer Institute, the Director of the National Institutes of Health, the Surgeon General the Bureau of the Budget, members of Congress and congressional committees as to special and general problems and progress in the field of cancer research, with specia

ROJECT DESCRIPTION (Continued)

J. reference to new developments and new opportunities, or to individual applicants and actions taken on their applications.

K. The carrying out of the broad policies established by the National Advisory Cancer Council and their interpretation as applied to individual cases, particularly as related to the most advantageous distribution of the limited funds available.

Summary of Actions: During the fiscal year 1955, research grant applications were presented to the National Advisory Cancer Council at its three meetings for review and recommendation as follows:

	Number	Amount
Applications reviewed	839	$10,348,525
Grants recommended	745	8,899,401

10. NCI-025
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See Appendix I & II

11.
BUDGET ACTIVITY

RESEARCH [ ] ADMINISTRATION [ ]

REVIEW & APPROVAL [X] TECHNICAL ASSISTANCE [ ]

12. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 or 1957: The Division of Research Grants, National Institutes of Health, provides the part-time services of personnel and of facilities for receipt of cancer research grant applications, their assignment, duplication and preliminary technical and scientific review by Study Sections, the processing for payment of approved grants upon authorization from the National Cancer Institute, and the fiscal audit thereof. Such activities are carried on in collaboration with the staff of the National Cancer Institute.

13. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:
This project parallels the research grant programs of the other categorical institutes of the National Institutes of Health and the non-categorical research grant program of the Division of Research Grants.

14. NCI-025
SERIAL NO.

15. PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1955:

None

16. HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1955:

1. Miss M. Catherine Vessels received a cash award of $150.00 for superior work performance.

2. Dr. Clinton C. Powell was reappointed a member of the American Hospital Association Committee on the Use of Radioisotopes in Hospitals.

APPENDIX I

The Research Grants Program assists scientific investigators in their attempts to discover the basic factors in the cancer problem as a means toward preventing, diagnosing and curing cancer. The major questions to which answers are sought include:

(a) What are the agents or conditions that initiate a cancer and through what mechanisms do they act?

(b) How can this process be prevented?

(c) What are the factors that promote cancer development and growth after it has been initiated?

(d) What are the characteristics of various types of cancer as distinguished from normal and benign growth, and of their effects upon the individuals in whom they grow, by which their existence and type can be identified?

(e) What means are effective to eradicate cancer or to control its growth?

As the partial answers to one or more of these questions are reported, they are rapidly applied to the solution of other questions. Some of the answers are of a nature that they can be applied to the social aspects of cancer in community life (control of environmental initiating agents, case-finding and diagnosis, therapy).

The major policy of the Public Health Service research grants program has been and continues to be that investigators select for themselves the areas of research in which they feel the most progress can be made with the qualifications they possess. Thus the investigators determine the subjects of study for which aid is requested and their proposals present a kaleidoscopic review of the field of cancer research. They represent the major determining factor as to the areas of research and the emphases that characterize the research grants program of the National Cancer Institute. Trends in cancer research usually reflect the collective thinking of active minds alert to new discoveries of phenomena or to the development of new techniques with which to re-explore previously known phenomena. The recommendations of the Study Sections and the National Advisory Cancer Council, and the decisions of the Surgeon General modify the collective approach of the scientists only insofar as they fail to provide Public Health Service support to research which may appear less promising scientifically or less significant to the problem of cancer. Fortunately, however, there are other sources of support for scientific proposals so that denial of aid from one agency does not necessarily mean a blockage of any study. Nevertheless, within the program of any one agency, it is possible that certain areas might appear to be little studied and it might be assumed that this was because of the bias of consultant scientists who recommend on the award of grants. Such a situation is unlikely to occur, however, because of the multiple review system which tends to modify, if not entirely correct, the effect

of biases. It is more likely that gap areas exist because of the lack of promising leads or methods by which to attack those problems.

In addition to the historic laissey-faire approach to scientific research which has generally been most productive of new ideas and techniques, the Public Health Service has on occasion followed the advice of its consultants in placing special emphasis on certain areas which appear ripe for exploitation or for which there appears to be special need. For example, when the development of new radiation instruments and atomic energy made study of the biological effects of high energy radiation feasible as well as an important problem in cancer induction and in cancer therapy, the National Cancer Institute participated in an attack on these problems by especially encouraging and supporting the work of scientists interested in this field. Throug various means, stimulus was given to interest and encourage scientists to extend their studies to include this modality in their experimental investigations. Similarly, when discoveries of chemical means of controlling growth of micro-organisms and of cancer cells suggested the possibility of discovering newer and better chemical agents for controlling cancer, the National Cancer Institute, on the advice of its consultants, undertook to encourage efforts in this direction by encouraging and supporting work of this type. The Congress made additional funds available for this purpose.

Grave concern has been expressed lest special emphases of the types just described lead to an imbalance in the natural evolution of research effort. The fear has been that this would lead to diversion of funds, manpower and facilities from areas of investigation that do not offer such immediate hope of beneficial knowledge applicable to the immediate control of disease. Such possible dangers must be recogn and overemphasis guarded against if there is to be a continued flow of new and basic knowledge into the reservoir from which come the fructifying ideas and techniques that may be applicable to practical problems like chemotherapy.

Although overenthusiasm for a certain area of study may temporarily unbalance and distort the relationship between study of fundamental phenomena and the application of limited knowledge to an immediate practical problem, there is usually a self-regulating corrective facto that eventually restores a new balance. This factor is composed primarily of the collective reaction of the scientists concerned and this is reflected in the changing opinions of consultants and their recommendati s regarding grants. Another element of the self-regulatory corrective factor is that enthusiasm wanes unless there are encouraging results from the newly emphasized program. Nevertheless, it is important for all concerned to be alert to the dangers of special emphases that may be ill-conceived or poorly executed, and that may temporarily interfer with other productive efforts.

This concern has been especially prominent in the expressed thoughts of some during the current fiscal year when the funds appropriated have been insufficient to permit support of all the worthy

recommended grants and yet special emphasis has been placed on chemotherapy by expansion of existing programs, and by stimulation of new groups, with support provided through additional funds earmarked by the Congress for this purpose. Although the wisdom of this method of earmarking by Congressional fiat rather than by the informed and balanced advice from consultants like the National Advisory Cancer Council may be questioned, there is not yet any evidence that the dangers of overemphasis have been created.

Analysis of the National Cancer Institute research grants program over a period of years reflects both the natural broad evolution of interest and capabilities of investigators who receive grants as well as the more abrupt fluctuations caused by special program emphases. For example, the percentages of funds for the broad areas, Carcinogenesis, Tumor Development and Clinical Studies, have changed but little over the past six years, although some increase in the funds for Clinical Studies has been evident in the past two years. Approximately one-third of the funds have gone into each of these areas. Nevertheless, when these broad areas are further broken down temporary fluctuations become noticeable. In 1950 the funds for Therapy, particularly Chemotherapy, were moderately high, apparently because of the support for studies evaluating antifolic agents. In 1951 the funds for Metabolism and for Endocrinology and Steroid Chemistry were increased; such an increase represants support made available for the evaluation of cortisone and ACTH. In 1952 and 1953 evaluation of high and supervoltage Radiation techniques led to increase in funds in this category. In 1954 a rather pronounced increases in funds available for the categories, Therapy, its sub-heading Chemotherapy, and Blood, resulted from the availability of additional monies for research in chemotherapy, with special emphasis on leukemia and related lymphomas.

The above information on the categorical distribution of funds is based on data for fiscal years. In fiscal year 1955 no particular change was noted compared with fiscal year 1954. Thirty-one per cent of funds was spent on studies in each category, Carcinogenesis and Tumor Development, and thirty-four per cent was spent for studies in the Clinical area. Among the different methods employed, Chemotherapy funds accounted for about one-fifth of total funds, and within the facet, Therapy, Chemotherapy accounted for sixty-two per cent of these funds. As regards funds for work done according to anatomical site, about one-fifth of these funds were for studies on Blood. Thirty-six per cent of the funds spent were not related to work associated with any particular site. The average amount per grant fell slightly from $12,888 in 1954 to $11,806 in 1955.

Data for the latter half of the calendar year 1955 have not yet been analyzed, but in view of the earmarked Congressional appropriation and increased activities of the Cancer Chemotherapy National Service Center, one could expect increased numbers of grants and increased funds for Chemotherapy studies during this period.

APPENDIX H

Research Accomplishments

Examples of research accomplishments from the different broad facets or areas of cancer research have been selected, and a few of them illustrate the type of study that is necessary for the enlargement of our reserve of basic knowledge upon which rest the ultimate practical applications for the cancer patient.

1) Investigations conducted by Dr. B. S. Oppenheimer of Columbia University on the possible cancer-causing properties of plastic films and other substances have yielded results showing high induction rates of malignant tumors in rats imbedded with some of these materials. Plastics in association with which tumors developed included Cellophane, Dacron, Ivalon, Kel-F, Nylon, polyethylene, polymethyl methacrylate, polystyrene, polyvinyl chloride, Saran, silastic, silk film, Teflon, and Vinyon N. Certain other related substances have not been shown to have this effect. Since tumors have been induced by both pure and impure samples, it is concluded that the polymer itself is the cancer-causing agent. The results depended to some extent on the physical form of the plastics used, which included plain and perforated films, textile fabrics, granules, sponge and powder. This work has now been confirmed by Drs. Edgar A. Bering, Jr., and Franc D. Ingraham and their associates at the Children's Medical Center of Boston. Tumors occurred in eight out of sixty-three rats when polyethylene sheets were implanted in the head and abdomen. The effect appears only at the site of contact and after periods of 434 to 738 days. The practical importance of this work results from the increasing use of similar plastic materials in reconstructive surgery. There is no evidence that similar tumors develop in humans who receive such plastic implants but the experimental studies have alerted surgeons to the consideration that such a possibility exists. These studies provide, also, further information on different classes of materials capable of inducing cancer in experimental animals. They may provide clues as to means for preventing the development of some types of cancer.

2) Further understanding of the role of excessive exposure to sunlight in causing skin cancers is promised by the work of Dr. A. Kelner of Brandeis University. It was found that the number of tumors produced by irradiating albino mice daily for several months with intense ultra-violet light could be reduced 50% by giving the animals a treatment of blue light immediately after each ultra-violet irradiation.

3) Further information regarding the factors that may cause cancer was recently uncovered during a study of the causes of gallbladder cancer. Drs. H. T. Randall and Joseph Fortner of the Sloan-Kettering Institute have found that bile may carry a substance which produces cancer specifically in the biliary system. In their experiments, whole whole bile from two patients suffering from carcinoma of the common bile duct was injected under the skin of 20 hamsters and 40 mice. Carcinoma of the bile duct appeared in two hamsters, and one mouse developed liver cancer. One hundred and twenty hamsters are being tested with bile from patients with cancer of the biliary tract, and

changes observed thus far include bile duct proliferation, cyst formation, necrosis and fibrosis of the liver. From the character of the changes observed, it is expected that cancers may develop in time. In sharp contrast, hamsters tested with bile from patients with non-malignant biliary tract disease showed only sloughing of the skin at injection sites and poor general condition. If these preliminary observations are confirmed, they will give added impetus to the search for metabolic errors in body chemistry which may lead to the production of chemicals capable of inducing cancer. This concept of cancer causation has long been under study. It suggests that if the errors can be recognized and understood, means can be devised for preventing or correcting them.

4) Antiserum against a breast tumor in mice has been developed by Drs. John J. Bittner, D. T. Imagawa, and J. T. Syverton of the University of Minnesota Medical School, using mouse tissue homogenates injected into rabbits and guinea pigs. The causative agent of this mammary tumor is neutralized by anitsera prepared against either cancerous or normal mammary tissue. Experiments with these antisera may point the way to progress against human breast cancer. Dr. Bittner has also studied the dependence of mammary cancer in mice on the interplay of various causative factors such as hormonal stimulation, hereditary influences, and the transmission of the tumor agent from mothers to suckling offspring via the milk.

5) The physical, chemical and biological properties of the virus which causes a type of blood cancer in chicks (erythromyeloblastic leukosis) are being investigated by Dr. Joseph W. Beard and his associates of the Duke University School of Medicine at Durham, North Carolina. It was found that birds injected with the virus develop an active immunity to the infectious process, depending on the amount of virus introduced and the route of inoculation. In other words, it is possible by injections to build up the resistance of chicks to this form of blood cancer. It has also been experimentally established that an enzyme associated with the release of muscle energy (adenosine-triphosphatase) is an intrinsic part of the virus particle. These studies are being extended to related forms of the chicken disease (lymphoblastic leukosis) and to the apparently somewhat similar forms of human disease (leukemia and lymphosarcoma).

6) Tumors arising in one individual are not normally transferable to another unless it be to an identical twin or (in animals) to a member of the same line which has been inbred long enough to make the individual members nearly as alike as identical twins. This situation is analogous to the problem commonly encountered in skin grafting. Normal tissues and tumors transplanted to an individual other than a fraternal twin or member of the same inbred line may grow for a time if there is some common relationship between the donor and the host but eventually they slough off. During this period, the host animal develops a resistance so that further transplants of the same tumor will not grow even briefly.

Induced resistance of this type and the natural resistance of host animals unrelated to the donor can be modified by prior treatment with irradiation, cortisone and other procedures which weaken or abolish the defense mechanisms of the host. In fact, new evidence is accumulating to show that extracts of normal or tumor tissue from an inbred mouse line that normally grows the tumor, when injected into mice of an inbred line that is normally resistant to growth of that tumor, will cause the previously resistant animals to become very susceptible to the tumor transplant and to enhance its growth.

Dr. George Snell, Dr. Nathan Kaliss and their associates at the Roscoe B. Jackson Memorial Laboratory at Bar Harbor, Maine, have been actively investigating this "enhancing effect" of tissue extracts and their nature. They have found more about the role of heredity in controlling the compatibility of tissues and about the immunologic reactions that modify the expression of this hereditary compatibility or incompatibility. Information has been obtained on the size and nature of the "enhancing material" by passing it through filters of known pore size. Eventually, it may be characterized chemically and physically. Studies of its know immunologic properties are being actively extended.

This work is an example of basic studies on the methods of expression of heredity and on the factors that modify susceptibility and resistance to foreign material whether it be tumors, infectious organisms, or normal tissue like skin. It has high potential significance for control of disease and for the repair of defects caused by accidents, such as burns, where skin grafting may be a serious problem. The primary interest of the investigators is in the nature of tumors and of the animals in which they appear but the results of their studies will probably have a much wider application in the problems of health, disease and repair of injury.

These last three studies represent those being carried on in an attempt to elucidate the role of viruses as causative agents in cancer, at least in animals, the part played by immunity in the resistance to cancer, and the genetic factors affecting this immunity. It is hoped that the better understanding of these factors in animal tumors may eventually help understand the nature of human cancer and how to control it.

7. It has been demonstrated previously by several investigators that bone marrow and spleen contain a substance which prevents death from whole body irradiation in animals and also inhibits the development of radiation-induced tumors of the lymphoid tissue (like leukemia) in mice. The nature of this substance is being investigated by Dr. Henry Kaplan and his associates at Stanford University Medical School. These scientists have learned, among other findings, that the active material is associated primarily with the nuclei of the cells of bone marrow and spleen. Further studies of the nature of this material are in progress.

Other studies are also in progress regarding the fundamental nature of the growth process, both normal growth and the abnormal growth seen in cancer. The understanding of this process and the ability of the body to control abnormal growth are represented by the following reports.

8) Viruses have certain attributes associated with the living cell. The bridge between life and inert substances was shown many years ago when a living virus was converted into a crystalline form like a non-living chemical and then shown to resume the attributes of life upon replacement in the proper environment. Dr. Robley C. Williams of the University of California and his associates have recently reported that it is now possible to separate such a virus into two major components which are different special chemical compounds, generally regarded as being components of living cells but not as being living themselves. Their most interesting observation is that when these two components are again mixed under proper conditions the virus reconstitutes itself so that it not only appears in the electron microscope as it did before being disintegrated, but is capable of infecting other cells and of reproducing, thus regaining some of the attributes of living material.

9) Three human cancers, including tumors of the skin and muscle, have been transplanted to the embryonic membranes of developing chicks, and cultivated successfully on the chorioallantoic membrane and yolk sac. Dr. David A. Karnofsky and his research group at the Sloan-Ketteri Institute for Cancer Research have found that human epidermoid (skin) cancer metastatizes to the embryo liver in about 25% of the chorioallantoic membrane transplants and in all of the yolk sac transplants. Chick carrying this tumor have been hatched, and when they were sacrificed several days later widespread metastases were found. No metastases from the other tumor types have been observed.

10) Dr. Edwin E. Osgood and John H. Brooke of the University of Oregon Medical School have reported for the first time the growth, for an indefinite period, of cells from human blood in tissue culture. Using newly devised culture media and special conditions, it has been possible to maintain strains of cells isolated from patients with leukemia. This development promises to expand greatly the possibilities for studying leukemia by permitting such studies outside the human body. It may make possible a more rapid and extensive survey of chemical agents that may be useful in the clinical treatment of leukemia.

Bearing on clinical aspects of cancer, the same investigators have also published further data indicating the effectiveness in prolonging the useful life of persons suffering from leukemia by their "titration" method of treatment. This method involves total body radiation, either by X-ray or radioactive phosphorus, in repeated small doses, using careful laboratory control to guide the timing of treatment instead of treating only when the patient's symptoms require

11) Among the most recently developed weapons against inoperable lung cancer, high voltage irradiation therapy is reported to have shown encouraging results. Dr. Ruth J. Guttman of the Francis Delafield Hospital in New York City has used two million volt therapy in 100 patients, 50 of whom had surgery of some kind prior to radiation therapy; the rest were considered to be clinically inoperable. Eighty-four patients were followed for more than three months and 63 of these showed definite benefit from irradiation therapy with respect to their symptoms. Twenty-seven patients have lived longer than one year, and of them, seventeen patients have survived two years and more. Twenty-four patients were living at the time Dr. Guttman's report was written, and of these 19 are completely symptom free. Age, sex and location of tumor do not seem to have any effect upon success or failure of therapy.

12) Both clinical radiation and surgery are significantly effective in the treatment of cancer, but there are few basic guides to indicate when one of these is to be preferred in therapy. In recent work Dr. John B. Graham and his associates at the Vincent Memorial Hospital in Boston have discovered a characteristic reaction in the cells of the vaginal mucosa which helps to determine whether or not a patient's uterine tumor will respond favorably to irradiation. Upon staining such cells obtained from the vaginal fluid with a special stain, they exhibit a deep lavender-staining protoplasm. Dr. Graham terms this localized phenomenon the sensitization response because in both laboratory animals and human beings the reaction is associated with increased sensitivity to effective irradiation. When 10% or more of the cells stain in this manner, the tumor is usually sensitive to irradiation. In 357 cases of uterine cervical cancer 30% gave a marked sensitization response; on the other hand, the response is rarely seen in the cells from vaginal smears of non-cancer patients, as indicated by an incidence of only 0.02% in 28,000 smears. A consistently better survival rate is noted in patients with cancer treated in the early stages by irradiation, and who have demonstrated strong response. Although poor response is associated with poor progress in radiologically treated lesions, a good prognosis is noted when such cancers are treated surgically.

13) How does a cancer cause the death of the host in which it grows? Why does a patient die with a small localized tumor without evidence of extensive destruction or of metastasis whereas a patient with a large and necrotic tumor and even with extensive distant metastases may survive for a much longer time, sometimes for years? An experimental attempt to clarify these questions has recently been reported by Dr Horace Goldie and associates at Meharry Medical College. Several different tumors were transplanted in mice to a variety of sites and with varied numbers of tumor cells. Some received transplants in a number of sites simultaneously but with the same total number of cells as for a single site. Also similar numbers of killed cells of some tumors were placed in the same sites. As might be expected, there was great variation but there occurred illustrations of the phenomena of early death in spite of the small amount of tumor tissue growth, and of late death of animals with large organized tumors. No damage was

evident from the injection of large numbers of dead or disintegrated tumor cells. It is suggested that the lethal effect of tumor cells is associated with their ability to grow and to infiltrate the tissues. The survival time of tumor bearing mice could be correlated with the pattern of spread of tumor cells from the primary growth. Multiple simultaneous inoculations and growth of tumors in many areas induced more abundant proliferation and earlier death. In all cases, the cause of death appeared to be associated primarily with the extent of infiltration of tissues and organs essential to life.

14) In another study aimed at the mechanism by which tumors may cause death, Drs. W. R. Bloor and Frances Haven at the University of Rochester have shown that in immature animals bearing a relatively slow growing tumor, starvation and consequent death occur because the intestine stops growing and is unable to receive and assimilate sufficient nutriment to feed both the tumor and the host. The intestine appears to stop growing soon after the tumor has become well established, while the tumor grows at the expense of the other tissues of the host. The manner in which the tumor adversely affects the growth of the intestine until it is inadequate to supply essential food constituents to both the tumor and the normal host tissues is possibly by using up certain materials from the intestine which would normally act through the pituitary and adrenal organs to stimulate progressive intestinal growth adequate to provide for the needs of the normally growing animal. A search for the nature and activity of this growth promoting material is in progress.

15) A correlation of bone marrow aspirations and skeletal roentgenograms has been made in clinical diagnoses of metastatic carcinoma by Dr. George A. Hyman of the Francis Delafield Hospital in New York City. While it is recognized that in advanced metastatic disease the bone marrow is frequently invaded, it is to be noted that marrow aspiration frequently afforded the only proof of metastatic carcinoma when other methods, including X-ray examinations, were negative. In this connection the marrow aspiration technique would seem to be of considerable value in indicating when useless and mutilating surgery can be avoided.

Although, as pointed out above, the cancer chemotherapy program is currently in the early stages of expansion, certain noteworthy studies have been reported as a result of work previously supported in this area.

16) A concerted attempt has been made to collect and make available in published form the experience of investigators in their unsuccessful searches for chemical agents which were originally considered to offer promising possibilities for control or destruction of cancer. The agents so evaluated have been recorded with the method of their trial and the results therefrom and have been published as supplements to the journal Cancer Research under the title "Negative data from experimental cancer chemotherapy studies." The second such

compilation has just appeared with the aid of a grant from the National Cancer Institute. The first compilation appeared in 1953. It should be emphasized that these data are "negative" only in the sense that they indicate positively a lack of any significant effect by the chemicals concerned on the growth of the tumors used as test objects under the conditions specified for the test. They do not necessarily prove a lack of significant effect for these chemicals for other types of tumors than those tested or for the same tumors under other conditions of trial.

17) Studies on combination chemotherapy of mouse sarcoma by Dr. D. A. Clarke of Sloan-Kettering Institute have shown that a definite interaction of drugs used in combination takes place in 55 out of 120 combinations tested. In some cases, the antitumor activity of one agent was actually blockaded by the administration of a second, but in other cases positive summation or even an increased potentiation was observed.

18) New chemicals which may be useful in the treatment of tumors of the prostate have been synthesized and tested by Dr. D. F. McDonald and Dr. T. L. Fletcher of the University of Washington. Sixty-two different compounds of more than a dozen different types were investigated; four of these, in the 9-iminofluorene series, gave impressive histologic regressive changes in the prostatic tumors.

19) The therapeutic effectiveness of triethylene melamine (TEM) in the clinical management of ovarian cancer has been studied by Dr. D. A. Karnofsky and his associates at the Sloan-Kettering Institute for Cancer Research in conjunction with Dr. R. W. Rundles of the Duke University School of Medicine. Twenty-six patients with far advanced and inoperable recurrent ovarian cancer were treated with this agent. Fourteen obtained some degree of symptomatic improvement, and of this group eight showed objective evidence of tumor regression. The usual duration of improvement ranged from one to three months. One patient showed an 11 month period of benefit and another has now shown no evidence of recurrent disease for a period of four years. The latter case may represent a spontaneous remission.

20) A new chemical compound belonging to the antibiotic group of drugs and called amicetin, appears to be of promising value in the chemotherapy of the leukemias. Dr. J. H. Burchenal and M. K. Dagg of the Sloan-Kettering Institute for Cancer Research in New York have obtained it from two molds, Streptomyces vinaceusdrappus and Streptomyces fasciculatus. Amicetin increased the survival time of mice inoculated with leukemia. Azaserine, a compound which has some effect alone on this leukemia, appeared to enhance the antileukemic action of amicetin when given in combination with it. One-quarter of the maximum tolerated dose of amicetin combined with one-quarter to one-half the maximum tolerated dose of azaserine seemed to be equally as effective as full doses of azaserine alone. Another compound, urethan, also prolonged the survival time of mice inoculated with leukemia.

PROJECT REPORT FORM

1. National Cancer Institute — INSTITUTE
2. Research Grants & Fellowships Branch — LABORATORY OR BRANCH
4. ____ — SERVICE OR SECTION
____ — LOCATION (IF OTHER THAN BETHESDA)
5. NCI-026 — SERIAL NO.

Administration of cancer research fellowships program
PROJECT TITLE

R. G. Meader
PRINCIPAL INVESTIGATOR(S)

Cancer Research Fellowships Specialty Board
OTHER INVESTIGATORS

PROJECT DESCRIPTION

Objectives: To encourage, promote, and support the research training of well-qualified candidates in basic science and clinical fields pertinent to cancer to the end that more and better qualified investigators will be enlisted in the attack on the problems of cancer at all levels.

Methods:

A. Provision of funds for the award of predoctoral, post-doctoral and special fellowships for training in research in fields pertinent to the problem of neoplastic growth.

B. Review by Central Qualification Board and Cancer Research Specialty Board of all applications submitted by candidates for fellowships in fields related to research on neoplastic growth.

C. Survey of the numbers, types, fields of study, subsequent activities and scientific progress of the candidates selected for support and of those not so selected.

D. Interviews with candidates and potential candidates.

E. Maintenance of liaison with the Office of Fellowships, Division of Research Grants, National Institutes of Health, through which the detailed administration of this program is effected and participation in the work of the Fellowships Boards in selecting candidates for the award of Fellowships.

F. Maintenance of liaison and exchange of information with other governmental and non-governmental agencies in this country and abroad with like interests, responsibilities, and programs in order to promote collaborative efforts and to avoid unnecessary and undesirable duplication of effort. Organizations of this type include the National Science Foundation, American Cancer Society,

PROJECT DESCRIPTION (Continued)

F. Damon Runyon Memorial Fund, Jane Coffin Childs Memorial Fund, Anna Fuller Fund, National Academy of Sciences and National Research Council, Rockefeller Foundation, Commonwealth Fund, the John and Mary R. Markle Foundation, and numerous others.

G. Preparation of special and regular reports for the information of the National Advisory Cancer Council, the Director of the National Cancer Institute, the Director of the National Institutes of Health, the Surgeon General, the Bureau of the Budget, members of Congress and congressional committees as to needs, activities, opportunities, etc. for training new recruits in the scientific areas germane to cancer research.

Summary of Actions:

During the calendar year 1955 there were awarded fellowships totalling $785,729 to 231 promising young scientists who are being aided by these funds to secure advanced research training in fields bearing on the cancer problem, including many aspects of biology, chemistry, physics, and medicine. These include predoctoral fellows undergoing training in research methods and conducting research that will lead to the granting of an advanced degree (Ph. D. or its equivalent) and a career in independent investigation. The remaining are postdoctoral and special fellows who are expanding their research training and experience under the supervision of or in association with a mature scientist preparatory to taking their places as investigators and teachers in the research and educational centers of the United States. It is the constant replenishment of the pool of research manpower which enables this nation to make continued progressin medical and scientific research. Nearly 90 percent of the scientists previously trained under this program are still actively engaged in research or teaching of medical subjects related to cancer. In addition to the promise of future contributions which the fellows in training offer, they are producing significant contributions while they are still in training.

During the year a new program was initiated in an attempt to give individuals interested in a research career the opportunity of earlier participation in an established research program. This program supported 241 part-time students with a total expenditure of $103,920.

10, NCI-026
SERIAL NO.

11. _____
BUDGET ACTIVITY

RESEARCH [ ] ADMINISTRATION [ ]

REVIEW & APPROVAL [X] TECHNICAL ASSISTANCE [ ]

12. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 or 1957:

The Office of Fellowships, Division of Research Grants, National Institutes of Health, provides the part-time services of personnel and of facilities for receipt of cancer research fellowship applications, their assignment, duplication, and preliminary review as to completeness, and for interviews when feasible. The Central Qualifications Board, comprised of representatives from other Institutes as well as the Chief of this Branch, reviews applications as to their satisfaction of minimum qualification requirements, aids in assignment of applications to the appropriate Specialty Fellowship Boards for review, and sets the range for stipends for special fellowships as guides to the Specialty Boards, thus assuring some degree of uniformity of action of the Specialty Boards. Staff scientist members of research Laboratories and of this Branch of the National Cancer Institute serve as members of the Cancer Research Specialty Board for review and recommendation as to award of Cancer Research Fellowships. The Division of Research Grants completes the award for the Surgeon General and processes approved awards for payment from fellowship funds of the National Cancer Institute, and the fiscal audit thereof.

13. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

This project parallels the research fellowships grant programs of the other categorical institutes of the National Institutes of Health and of the non-categorical program of the Division of Research Grants but differs in the fields in which fellowships are awarded. Staff scientist members of research laboratories and of this Branch of the National Cancer Institute serve as members of the Cancer Research Specialty Board for review and recommendation as to award of Cancer Research Fellowships. The Division of Research Grants completes the award for the Surgeon General and processes approved awards for payment from fellowship funds of the National Cancer Institute, and the fiscal audit thereof.

NO ENTRIES FOR 14,15,16.

INTRAMURAL RESEARCH

NATIONAL CANCER INSTITUTE

1955

INTRODUCTION

This is a chronicle of selected accomplishments by the research staff of the National Cancer Institute during calendar year 1955. Substantial progress continues to be made. Steady increase in clinical activities during the period covered by the report has increased the proportion of the total resources committed to therapeutic investigations. The preponderance of patients admitted to NCI beds suffer from advanced, disseminated cancers. This type of patient represents, of course, a major problem in cancer control and a fit subject for research. The same factors that limit progress of research in preclinical areas are already obvious in the clinic. The more one studies cancer, the more dependent one becomes on advances in biology, biochemistry, biophysics and related fields of science.

Such practical considerations as space, budget and availability of talented investigators will probably prevent a major increase in direct NCI commitments to basic research in the immediate future. The mean age of principal investigators in most of the older laboratories is steadily increasing. It becomes imperative to recruit young scientists to provide continuity of effort among those programs making real contributions of critically needed information. A first step requires decisions as to those enterprises which seem to be most profitable or likely to become so through recent advances in knowledge. The recruitment activity then becomes possible only if substantial increases in moneys available to preclinical areas can be provided.

The costs of research are increasing. A much needed increase in pay scale during the year is partly responsible, but equally noteworthy is the higher cost of consumable supplies due to changes in activities as the result of research progress. The availability of optically active, pure amino acids suggests important and heretofore impossible excursions in the fields of protein chemistry and metabolism. The tools, however, are costly and even more expensive are the filterable viruses that have been introduced into clinical therapeutic research. A large fraction of any new moneys provided by the budget for fiscal year 1957 should be added to "other objects" accounts.

Several members of the professional staff have left NCI during the year. The majority have obtained positions of major responsibility at salaries appreciably greater than government affords. These talented and highly productive investigators will be sorely missed.

There have been a number of organizational changes of late. The Institute has been fortunate in obtaining the services of Dr. J. Robert Andrews, formerly Professor of Radiology at Bowman Gray School of Medicine, as Chief, Radiation Branch, thereby greatly strengthening the program in radiation research, particularly as it applies to problems associated with the management of neoplastic diseases. A Laboratory of Physiology was created, Dr. Julius White, Chief, to stimulate research in the influence of cancer on its host. A new Section on Physical Chemistry and Chromatography, Dr. Herbert A. Sober, Head, was organized in the Laboratory of Biochemisty, and important organizational changes were also made in the Laboratory of Chemical Pharmacology.

Well deserved recognition was accorded two members of the scientific staff. Dr. Lloyd W. Law, Head, Leukemia Studies Section, Laboratory of Biology, received the first Anne Frankel Rosenthal Award for Cancer Research. Dr. Harvey A. Itano, Laboratory of Biochemistry, delivered the George Minot lecture before the Section on Experimental Medicine and Therapeutics of the American Medical Association in June. Many of the staff have participated in important national and international meetings and symposia. Dr. Harold L. Stewart, Chief, Laboratory of Pathology, engaged in a discussion on research on Cell Biology sponsored by UNESCO at Paris in December.

The body of this report is organized along functional lines to show the co-operation among physicians and scientists as they approach the study of problems important to the ultimate control of cancer. It cannot do justice, however, to the enthusiasm and devotion to duty that the participants exhibit in pioneering beyond the frontiers of human knowledge.

CAUSATION OF CANCER

Extrinsic Agents

Few of the many agents available for the production of cancers in laboratory animals elicit neoplasms in every member of a species. Reactions of individuals to their environment are regulated in part by heritable traits that remain to be defined in precise terms. Identification of those environmental agents which increase the risk to cancers in man permits elimination of such hazards from human experience. Laboratory investigation affords opportunities to establish cause and effect relationships and provides, at present, the only practical means of pursuing the course of events from initiating stimulus to overt cancer. The ultimate prevention of

cancers depends almost solely on this type of activity.

Chemical compounds: Cancers of the urinary bladder constitute an important segment of neoplastic diseases. A small fraction of these lesions are due to exposure to known chemical compounds such as benzidine and β-naphthylamine. Research in Great Britain provides strong evidence that the latter agent is altered by the body to produce another compound, 2-amino-1-naphthol, which actually causes the cancers in the urinary bladder. While the generality of patients with bladder cancers have not been exposed to the noxious agents used in certain industrial processes, a possibility exists that other compounds more common to human experience may be changed to 2-amino-1-naphthol by the body. Two compounds related to β-naphthylamine are known to be ingested by man. Drs. W. C. Hueper and P. L. Malloy have found that urine of patients fed one of the agents gives a color test for 2-amino-1-naphthol. The specificity of the color reaction is in question and it will be necessary to isolate the reactant and prove its identity by other means.

Studies on the causation of human cancer of the lung have reached the point where several mixtures with which the populace has continuing contact are known to elicit some cancers in experimental animals. The problem of assaying the relative importance of these agents in the genesis of bronchogenic carcinoma is highly important. Systematic attempts to reproduce pulmonary cancers at all comparable to the major types found in man have been largely unsuccessful. The ability of known carcinogenic hydrocarbons to elicit neoplasms in embryonal tissue transplanted to adult animals is a rather sensitive test of carcinogenic potency. Dr. C. Harold Steffee obtained 10 malignant neoplasms arising from embryonic lung which was transplanted with a crystal of methylcholanthrene. Repetition of the work in which condensates of cigarette smoke were substituted for methylcholanthrene failed to yield neoplasms in any of the 13 cases studied.

Long term inhalation studies of rats exposed to chromite ore dusts continue under the direction of Dr. W. C. Hueper but no pulmonary cancers have developed. The importance of chromate cancer of the lung has led to studies by Dr. C. H. Grogan on the fate and distribution of this element in tissues and body fluids as a means of further investigating cause and effect relationships in man. All the chromium found in blood, urine and tissues can be accounted for by oxidative solubilization of chromite ore originally inhaled and deposited in lung tissues. The upper limit of particle size that can be inhaled is 5 microns, hence particle size becomes critically important in exposure as the concentration of chromium in tissues becomes higher. Particles of 4 microns diameter or less form a larger proportion of the dust. These findings controvert the previously held opinion that chromium in chromite ores is metabolically inert.

Among the substances used as "plasma expanders" to combat shock are two classes of polymeric compounds, one synthetic, polyvinylpyrrolidone, the other a natural product, dextran. Dr. Hueper has injected into rats, rabbits and mice polyvinylpyrrolidones or dextrans covering wide ranges of molecular weights. About 30 percent of rats dying during the first 18 months which received subcutaneous, intraperitoneal or intravenous doses of polyvinylpyrrolidone have developed malignant neoplasms of the reticulo-endothelial system. Most of the tumors arose in lymph nodes and some produced a widespread leukemia; some arose in the Kupffer cells of the liver; a few rats developed uterine neoplasms. None of the other species receiving comparable amounts of polyvinylpyrrolidones have developed any neoplasms more than one year after exposure, nor have tumors appeared in any of the rats, mice or rabbits injected with dextran that can be attributed to the experimental procedure.

Research in cancer causation usually requires prolonged studies of effects of agents on experimental animals. Sufficient experience has accumulated with some classes of chemicals so that identification of specific compounds in a mixture suspected of causing cancer in man may give important information. The carcinogenic hydrocarbon 3, 4-benzpyrene, for example, occurs in several different types of environment which have been incriminated in the causation of human cancers of the skin. Dr. E. J. Cahnmann has developed new methods employing partially activated gels for separating and identifying compounds chemically related to the carcinogens. Some of these substances can be recovered from oysters obtained from contaminated waters. Such molluscs are known to be unfit for human consumption and, like barnacles, seem to be able to concentrate dangerous contaminants in their substance. One by-product of Dr. Cahnmann's work included the isolation and identification of a new or rare sterol.

Dr. M. D. Barrett reports increase in the frequency of hemangioendotheliomas in mice by subcutaneous injections of o-aminoazotoluene both in genetically susceptible and resistant subjects. Dr. Heston reports a greater frequency of hepatic tumors among C3H mice receiving urethane, a compound known to produce pulmonary neoplasms both in mice and rats.

Ionizing radiations: X-rays are known to be important carcinogenic agents and earlier accounts have considered the occurrence of leukemias in mice rather large doses of total body irradiation in short periods of time. Mrs. J. W. Hollcroft, Miss Eliza Miller and Dr. C. C. Congdon previously noted an increase in leukemia and mammary tumors among mice receiving daily doses of 0.11 r of gamma rays from radium. The life span was not decreased. The same investigators now report experience with guinea pigs in which anemia was produced by chronic exposure to daily doses of 8.8 r of gamma rays from radium. The degree of anemia was approximately constant when the animals were removed from the radiation field but the

guinea pigs ultimately developing leukemia exhibited even greater degrees of anemia than did those which did not become leukemic. The guinea pigs in this experiment were all protected from early death by intravenous injection of bone marrow which, of itself, had no pronounced effect on the incidence of leukemias.

These investigators studied the influence of 400 and 900 r total body X-irradiation of newborn mice on tumor production. The spleens of some of the mice were shielded to minimize acute toxicity but neither spleen shielding nor the fact that the subjects were irradiated at birth had any observable influence on survival time. Lesions noted to be increased among the newborn mice receiving 900 r included cataracts, tumors of the adrenal glands and ovaries, and severe damage to the kidneys and bone marrow.

Exposure of rats eating a relatively low protein diet to total body irradiation has previously been reported by Dr. J. White to produce cirrhosis of the liver. Addition of choline to the diet completely prevents this development and constitutes the first evidence that X-irradiation influences the metabolism of methyl groups important in many metabolic processes. Drs. R. C. MacCardle and C. C. Congdon find that X-rays produce definite changes in the mitochondria of mouse liver cells. The mitochondria recover their normal appearance after injection of bone marrow.

Dr. R. C. MacCardle has studied pituitary tumors provided by Dr. J. Furth (Children's Medical Research Center, Boston, Massachusetts). These neoplasms follow destruction of the thyroid gland usually by administration of radioactive iodine. They can also be produced by thyroidectomy. The lesions have the curious property of secreting large quantities of thyrotrophic hormone, a normal product of hypophyseal metabolism necessary for the proper functioning of the thyroid. Dr. MacCardle finds that the tumors appear to be derived by a change in alpha cells. The Golgi apparatus within the cell enlarges and develops an affinity for metals as more cytoplasmic iron b ecomes deposited in its vicinity. The mitochondria also develop certain new qualities since they are destained with greater difficulty than are mitochondria in normal cells of the pituitary body.

Intrinsic Agents

Hormones: The occurrence of mammary tumors in mice after administration of estrogen has long been established. Male mice which never develop cancer of the breast under ordinary circumstances can be made to develop such lesions by treatment with female sex hormone but only if the mice are genetically susceptible. Progesterone is a hormone characteristic of the corpus luteum which forms after the ovum has been extruded from its follicle. Production of progesterone is sharply limited if pregnancy does not ensue, but the hormone assumes major importance during pregnancy when its production is maintained for a prolonged period. The action of a given

dose of estrogen is for the most part more prolonged than is a comparable amount of progesterone, and some biological activities of these two hormones are antagonistic; others, complementary. Lacassagne suggested, some years ago, that the formation of corpora lutea was concerned in the causation of mammary cancers in some mice. Greatly increased support for this concept is afforded by the observation of Dr. H. B. Andervont that combined treatment of C3H mice with both estrogen and progesterone results in the development of more cancers of the breast than does estrogen treatment alone. This introduces an important new factor into the causation of mammary neoplasms.

Dr. Andervont has also continued his studies of tumors of the interstitial cells of the testis that follow prolonged estrogen administration to certain male mice. Last year's report included evidence of an effect of the agent on some of the biological characteristics of these lesions since removal of the stimulus was sometimes followed by regression of the tumor, which reappeared on renewed treatment. It was also shown that the neoplasms persisting on withdrawal of the stimulus were usually capable of growing in other appropriate mice in the absence of the initiating estrogen. Dr. Andervont now reports that the longer transplantation of interstitial cell tumors is delayed from their gross inception the larger is the proportion of the lesions that will grow independently. Conversely, more of the tumors transplanted soon after their initial appearance require estrogenization of the recipient for continued growth and evolution. No structural differences between dependent and independent neoplasms are recognized. Undesirable toxic reactions to estrogen seem to be greatest at earlier ages.

Filterable viruses and cell-free tissue extracts: An agent possessing many of the attributes usually associated with filterable viruses occurs in the milk of lactating mice and influences strongly the occurrence of mammary cancers in their progeny some months later. Strains of mice rendered free of the milk agent by foster-nursing have been developed both by Dr. Andervont and Dr. W. E. Heston. Dr. Andervont's agent-free mice develop mammary neoplasms in only 6 percent, but the agent-free strain of Dr. Heston has an incidence of cancers of the breast of 25 percent at an average age of 20 months. They are now in their 29th and 30th generations since the milk agent was removed and, unlike mice known to possess the agent, show no tendency for their mammary tumors to become segregated along familial lines.

The occurrence of neoplasms of the salivary glands, pricipally parotid in origin, that followed injection of cell-free tissue extracts into newborn mice was reported earlier. Dr. L. W. Law has extended his observations to include several hybrid derivations of the C3H strain. He has noted the occurrence of highly invasive subcutaneous tumors of a different histological type arising, like the parotid tumors, months after injection of the cell-free material.

A transplantable tumor of the medullary portion of the adrenal gland gave rise to neoplasms of the parotid in 40 percent of its hosts through 8 successive transplant generations. This power was subsequently lost. Dr. S. E. Stewart describes several different transplantable neoplasms from which cell-free extracts can be obtained that frequently yield parotid tumors when injected into appropriate subjects.

Dr. Stewart also reports additional characteristics of these unusual neoplasms. One type of structure can be perpetuated by serial transplantation into mice that have received total body irradiation. Growth is accompanied by changes indicating a marked increase in blood volume. The tumors grow more slowly and less frequently in unirradiated mice of the same strain and assume the appearance of sarcomas without obvious increase in blood volume.

Drs. L. W. Law and T. B. Dunn have reported studies on the pathogenesis and histogenesis of the parotid tumors.

While the nature of the material responsible for the production of neoplasms in salivary glands has not yet been identified, it would appear that more than one infectious agent may be obtained from some transplantable leukemias.

Genetic Influences

Susceptibility and resistance to carcinogenic stimuli are controlled by heritable traits to the extent that very few potent carcinogenic agents evoke a cancerous response in all exposed members of a heterogeneous population. The precise nature of the genetic qualities associated with increased or decreased risk to cancer has not been defined, but they seem to reside in specific organs or tissues. Research in this area correlates genic composition with liability to one or another specific type of neoplasm and with certain identifiable non-neoplastic characteristics.

Dr. M. D. Barrett reports a decreased susceptibility to pulmonary tumors induced by a carcinogenic hydrocarbon among mice possessing the fused tail gene. Caracul and dominant spotting genes have no influence on the occurrence of induced neoplasms of the lung. The same situation was reported previously for spontaneous pulmonary tumors, hence the genetic mechanisms eliciting both types of tumor production seem to be essentially similar.

An association between the yellow gene (A^y) which leads to obesity and the heightened frequency of pulmonary tumors reported earlier by Dr. W. E. Heston has led to further study to determine whether or not the lethal yellow gene itself increases the incidence of pulmonary tumors or acts through some general effect related to obesity. Dr. Heston has treated closely related mice that do not possess the A^y gene with gold sodium thioglucose which causes pronounced increase in body weight. Mice rendered obese by this method

developed as many induced pulmonary tumors as did those made fat solely by the genetic influences of the lethal yellow gene.

Genetic research will be materially advanced by correlation between physiological or biochemical events and identifiable heritable factors. Dr. G. L. Wolff (Research Fellow) is studying effects of genes causing obesity on metabolism. The Harding-Passey melanoma becomes established most rapidly in female mice possessing ob ob genes. The glycolytic metabolism in this particular type of mouse seems much higher than in other subjects possessing varying combinations of the ob, Ob and AY genes and probably favors the growth of cancers in which glycolysis is generally considered an important source of producing energy from carbohydrate. The anaerobic glycolysis of the Harding-Passey melanoma is higher when grown in female mice possessing ob ob than in any of the other sex-genotypes studied.

An excellent example of genetic influences on tumor production is afforded by work of Dr. Michael Potter. Certain types of cancers occur most frequently at relatively specific ages both in man and experimental animals. Death from a cancer occurring in early life precludes any opportunity for development of other types of neoplasm. Dr. Jacob Furth (Children's Medical Research Center, Boston, Massachusetts) reported in 1946 that a few tumors of bone, called osteomas, occurred in old AK mice. This particular strain has extremely high incidence of spontaneous leukemias. The first filial generation of the progeny from matings of C3H and AK mice bred by Dr. Potter had a high incidence of osteomas, especially in females. Cross breeding between AK and Sto-Li mice yielded similar though less striking results. Dr. Potter has made another tumor-type available for study and has already demonstrated strong genetic influences in the origin of these lesions.

Mechanisms of Cancer Production

Ability to produce one or another specific type of cancer with a high degree of reproducibility permits research on the intricacies of the carcinogenic response. This type of enterprise takes two general directions in the NCI program: 1. Precise definition of factors involved in development of a morbid state. 2. The means by which a given carcinogenic agent produces its effect.

Removal of the thymus gland in mice with high risk to development of leukemia almost eliminates that risk. The probability of contracting leukemia is restored if fragments of thymic tissue be transplanted to the subcutaneous tissues after the subject's own thymus has been extirpated, but only if the donor graft is obtained from a genetically appropriate mouse with a high risk to spontaneous leukemia. Thymic tissue from low incidence lines has no such influence. Additional work by Dr. L. W. Law indicates that the leukemia occurring in the thymectomized subject usually arises in the grafted fragment. The thymic influence seems to be most potent in respect

to leukemias arising from lymphoid cells since some reticulum cell sarcomas have been found among thymectomized mice though they arise comparatively late in life.

X-irradiation produces leukemia both in man and laboratory animals. Dr. Law has extended his work on the thymus to include radiation-induced leukemias. Removal of the organ completely prevents induction of lymphocytic neoplasms by X-rays, but reticulum cell tumors do occur. Thymic tissue grafted from appropriate mice within a short period following exposure of the thymectomized subject to X-irradiation restores the high risk to leukemia in about 30 percent of cases even though the graft itself was not radiated. The leukemias occurring within 6 months apparently arise from cells introduced by the graft, whereas the leukemias occurring at 8 to 10 months after exposure to X-rays originate from the host. These results provide additional information, as originally suggested by Dr. H. S. Kaplan (Stanford University), on an "indirect mechanism of X-ray induction" in leukemia depending on a post-irradiation state. They also indicate quite clearly an important and unsuspected role of the thymus gland in genesis of leukemia not necessarily related primarily to its availability as a common site for origin of the disease.

The program on production of different types of cancers by 2-acetylaminofluorene and related compounds has made substantial progress during the year under the leadership of Dr. H. P. Morris. Dr. Morris and Dr. H. I. Firminger (University of Kansas) have produced hepatomas in rats within 6 weeks by continuous feeding of 2-acetylaminofluorene. Most of the lesions occur in male rats or castrated males receiving male sex hormone, suggesting that androgen has an important influence on the carcinogenic potency of 2-acetylaminofluorene for the liver. Dr. Morris also finds that intake of the vitamin riboflavin has little influence on the production of hepatic tumors with 2-acetylaminofluorene though others have reported that riboflavin intake strongly influences the capacity of p-dimethylaminoazobenzene to induce cancer in the liver. Dr. Morris did find some influence of the vitamin, however, on the occurrence of other types of cancers that occur in rats ingesting 2-acetylaminofluorene. Drs. J. H. and E. K. Weisburger have identified two more urinary metabolites of 2-acetylaminofluorene. Others have established that bladder cancers can be produced with this compound by adding the amino acid tryptophan to the diet. The Weisburgers find no evidence that this procedure markedly modifies the quality of urinary metabolites of 2-acetylaminofluorene. Dr. H. M. Dyer is studying the binding of carcinogenic agents by the liver as a fundamental step in producing cancer, as suggested by the Drs. Miller (University of Wisconsin). Two potent agents related to 2-acetylaminofluorene are tightly bound by hepatic proteins to the same extent as the prototype but another analogue with little or no carcinogen power is not bound.

ATTRIBUTES OF THE CANCEROUS STATE

Classification of malignant neoplasms by pathologists has provided the medical profession with valuable information of practical import. Correlation between structure and function is sufficiently good to serve as general guidelines for treatment and to permit analyses of therapeutic results if one deals with comparatively large groups of specific anatomical types of cancer. The physician finds it practically impossible, however, to anticipate the course of many kinds of cancer in individual patients. Morphologically similar, even identical, neoplasms may diverge widely in their clinical behavior, which necessarily reflects important biological and biochemical differences in their attributes.

Intensive efforts in describing important characteristics among cancers grown under controlled circumstances have led to marked progress in cancer research. Each new advance, however, emphasizes the crying need for additional information obtainable only from very basic studies of the nature of protoplasm, chemical reactions among metabolically important compounds, in short, the entire biology, biochemistry and biophysics of normal growth processes. Some of these require study of organisms lower in the evolutionary process than mammalia, the exploration of isolated systems in artificially created environments and other pursuits of knowledge not directly related to the cancerous state. The critically important information sought by diverse approaches furthers the attack on practical problems of cancer.

Tissue Culture

The utility of tissue culture as a tool for the study of cancer has already been greatly enhanced by the technological advances of Dr. W. R. Earle and associates who devised practical means of growing relatively large quantities of cells under controlled conditions. Work during the past year has provided an adequate medium for the growth of strain L cells which contains known chemical only. Dr. V. J. Evans and her colleagues have observed continued good growth for as long as 11 months in the completely derived medium which is now being simplified. The growth requirements of individual cell types seem to vary. The chemical medium for strain L cells does not support good growth of all cell types, but addition of less than 1 percent of protein makes the medium suitable for a variety of cells. The protein, according to Dr. B. B. Westfall, can be provided by horse serum, and the greatest activity resides in globulins other than those possessing the characteristics of gamma globulins.

Production of the chemically derived medium is facilitated by studies on chemical changes in the fluid bathing the cells during the course of their growth. The medium originally contains small quantities of alpha keto acids, important intermediary compounds

both in carbohydrate and protein metabolism. Dr. Westfall and others report that good cell growth increases the level of alpha keto acids to that found in plasma of mammals. Amino acids are exhausted within 3 days if their concentration be low and reduction in glucose content precedes cessation of strain L growth in shaking culture.

The production of cancer among cells grown in tissue culture was accomplished years ago. Repeated experience has shown marked decrease in ability of the cells to produce neoplasms when retransplanted to suitable intact hosts with increasing residence in vitro. Total body X-irradiation usually enhances the capacity of these altered cells to elicit cancers in mice. Shortness of the latent interval between transplantation and the appearance of the tumor suggests strongly that the lesion arises from multiplication of the inoculated cells rather than through some effect on the host's own tissues. Substantial information on the reasons for these peculiar phenomena has accumulated. Drs. V. J. Evans, Miss N. M. Hawkins and Dr. W. R. Earle have studied a culture which yields no more than 1 percent sarcomas when introduced into appropriate irradiated or untreated mice. Reculture of a tumor that arose produced colonies eliciting sarcomas in most of the mice to which it was retransplanted, whereas introduction of fragments from the tumor directly into genetically suitable mice, instead of into tissue culture, produced sarcomas much more frequently in irradiated than in non-irradiated subjects. This complicated situation cannot be completely explained at this time, but experiments reported by Dr. Katherine Sanford, Mrs. G. L. Hobbs and Dr. W. R. Earle shed some light on an important point. A clone culture of strain L cells that produced sarcomas in more than one half of C3H mice into which they were transplanted now elicits neoplasms infrequently. The cells after years in tissue culture stimulate defense mechanisms in the strain from which they were originally derived. An increasing degree of foreignness would seem to be developing which prevents the cells from producing tumors, hence reduction in their tumor-producing capacity need not reflect change in the malignant characteristics themselves.

Dr. Sanford and her co-workers have studied two lines of cells derived originally from one single cell isolated in tissue culture which differ markedly in their ability to produce tumors. The capacity for sarcoma formation depends on the number of cells forming the inoculum and is influenced by duration of growth outside of the animal body. Both lines are antigenic and demonstrate cross immune reactions since hosts rendered resistant to one of the lines will not grow cells of the other line. Pronounced differences in the latent period of tumor formation characterize the two and their malignancy can be enhanced by serial transplantation in C3H mice. In spite of these dramatic differences both lines proliferate at the same rate in vitro.

Dr. Joseph Leighton has observed the transformation of human preputial fibroblasts into a structural pattern characteristic of fibrosarcoma after residence in sponge-matrix tissue culture for little more than 2 years. Examination of so-called normal cell lines originating elsewhere reveal morphological qualities usually associated with cancers. The evaluation of purely structural aberrations without other frames of reference is hazardous at best. Pathologic diagnosis represents the development of long experience accumulated over the years by many trained observers of anatomical patterns, both gross and microscopic, which are consistently correlated with clinical manifestations of disease. The tissue culturist has no way of learning the complete significance of the changes occurring during in vitro growth without reintroducing his cells to their normal environment. The animal experimentalist finds this easy to do but he who works with human cells must exercise great ingenuity in devising model systems by which the biological attributes of the altered cells may be determined. Cancerous cells possess an almost unique ability to invade and destroy normal tissues. The three-dimensional sponge matrix method of tissue culture devised by Dr. Leighton enables him to measure objectively the invasive properties of human cells known to be cancerous, and with Dr. Morris Belkin he has made real progress in studying this important problem.

Not all cells, nor even cells from all cancers, will grow well in tissue culture. Leukemic cells, in general, survive comparatively short periods under the most favorable circumstances. Dr. C. J. Dawe finds it possible to almost double the normal survival time of leukemic leucocytes from mice in vitro. Dr. W. E. Mohler reports that only 5 of the 10 clinical cancers he studied could be grown readily with tissue culture methods now available.

By-products of cancer research continually contribute importantly to the total efforts in biological and medical research. Grafting of corneas has become a reality but the supply of suitable material for grafting is strictly limited. Drs. W. R. Earle and V. J. Evans, co-operating with members of the staff, National Naval Medical Center, have found a practical means of preserving rabbit corneas for at least 6 months in a completely viable state. Skin, unfortunately, cannot be preserved in the same manner.

Transplantation Studies

Dr. L. S. Lombard, who recently jointed the Laboratory of Pathology, has brought to NCI a transplantable canine thyroid tumor which can be propagated serially in X-irradiated puppies. It has been observed through 35 transplanted generations, retains its original structure essentially unaltered and continues to metastasize both to lungs and lumph nodes. Cancer research would benefit materially by the ability to use larger animals than conventional laboratory rodents, especially in those approaches requiring continuing analysis of blood and other body fluids, development of surgical

techniques and certain aspects of pharmacology.

Renewed interest in the growth of human cancerous tissue in foreign species has been attended by varying degrees of success in several institutions. Dr. C. H. Steffee and Dr. K. C. Snell recognized the possibility of transplanting human fetal tissues to hamsters as a means of furthering the experimental production of pulmonary cancers. Existing data suggested that the natural resistance of the species to growth of foreign tissues might be overcome by administration of cortisone. Dissecting aneurysm of the aorta proved to be a major complicating factor associated with the cortisone treatment. Suggestion that adrenal hormones may be causally related to the aortic lesions is reinforced by Dr. T. B. Dunn's description of similar lesions in mice bearing a transplanted functional carcinoma of the adrenal cortex.

Correlations between structure and function have been greatly facilitated by the ability of malignant neoplasms to grow progressively on transplantation to genetically appropriate subjects. Failure of some pulmonary tumors to grow on transfer to members of the same inbred strain suggested systematic study of transplantability of these neoplasms, and Dr. C. H. Steffee reports that such lesions must reach a critical size before they become readily transplantable. This work should be extended as one means of exploring in greater detail the evolution of biological attributes of cancers not necessarily reflected by morphological alterations.

Some pulmonary tumors of mice which appear characteristically epithelial develop as typical sarcomas on serial transplantation. Dr. Steffee presents evidence that the sarcomatous appearing lesions are derived from the original transplanted tumor cells rather than from the host's own tissues.

Dr. R. T. Prehn has extended his studies on transplantation of genetically incompatible skin by delivering large doses of total body irradiation to the recipient of the graft and protecting it from acute lethal effect through intravenous administration of bone marrow cells. Additional donors of different genetic constitution have proved suitable. The source of the injected marrow determines in large degree the genetic derivation of the skin that will be tolerated. Treatment with bone marrow cells from DBA mice, for example, will permit an original graft, or even a subsequent graft, from DBA strain mice to survive and grow indefinitely but will not allow successful transplantation of skin from C57 black mice. Skin grown in the treated mouse may be retransplanted to its original strain.

Dr. R. M. Merwin has partially characterized the marrow cells that protect mice against lethal doses of X-rays. Her studies indicate that the marrow which regenerates after total body irradiation has genetic attributes associated with the donor rather than the recipient. Possibly the marrow spaces become repopulated by the injected cells, but the experiments thus far reported involve an a assumption that X-rays have no important influence on the genetic

constitution of the irradiated subject. The experiments of Dr. Prehn can be interpreted contrariwise.

An alternative mechanism by which transplanted marrow cells provide protection against lethal doses of total body X-irradiation is elaboration of some important material into the circulating blood. Diffusion chambers designed by Dr. G. H. Algire permit exploration of that possibility because the walls of the chamber can be made to exclude passage of cells but allow permeation by smaller substances. No protection is afforded by twice the minimum effective dose of marrow cells encased in intraperitoneal diffusion chambers. Relationships between minimum effective dose in terms of numbers of cells are now found to require a critical volume to exert their action, hence Dr. Algire s results are preliminary in nature.

Dr. R. M. Merwin described vascularization of normal tissue grafts as a process including proliferation of capillaries in both the graft and the recipient's tissues. Cancerous transplants now appear to derive their blood vascular system solely from the host s vessels. This seems to be a clearcut difference between normal and cancerous tissues.

Endocrinological Studies

Many hormones are powerful catalysts which alter structure and function by permitting certain biochemical reactions to proceed at higher rates. Not all organs and tissues respond to hormonal stimulation, but endocrinology has contributed importantly both to knowledge of causation of cancer and the management of some cancerous patients. "Target" organs, those most altered by hormone stimulation, are commonly associated with reproductive functions. The "target" organs require hormonal stimulation of some degree for their structural and functional integrity, but post-natal development includes a period when the primary and secondary sexual apparatus fail to respond to endocrinological stimuli as they do in later life. Dr. Roy Hertz and Mr. D. B. Spencer, studying the development of the ovary in infantile rats and rabbits, find it refractory to stimulation by gonadotrophin, secreted by the pituitary gland, until the ovarian follicles form antra. The response characteristic of the adult ovary can readily be elicited thereafter by gonadotrophin. The pituitary hormones seem to be only one factor in post-natal development because infantile ovaries grafted to the mother s kidney will undergo normal differentiation even though she be hypophysectomized.

The same investigators have devised a means of assaying luteinizing hormone. Hypophysectomy during pre-estrus aborts succeeding ovulation which depends entirely on the presence of luteinizing hormone in the rat. If the material under test contains sufficient amount of luteinizing hormone the capacity to ovulate is restored.

Certain qualities of certain hormones seem to overlap one another. Ability to stimulate proliferation of the endometrium, the lining of the uterine cavity, is shared by some compounds which simulate activity of the adrenal cortex. Dr. Hertz and his colleagues find no progestational effect from hydrocortisone which influences adrenal cortical activity importantly. Introduction of a fluorine atom into the molecule at the 9 position increases corticoid potency and imparts progestational activity in both the monkey and rabbit. Fluorination of 11 beta-hydroxyprogesterone increases progestational activity similarly. These new compounds which share depressant capacity of corticoids and at the same time stimulate proliferation of epithelial cells may shed some light on structural derangements of the uterine mucosa associated perhaps with the development of cancer.

Dr. E. M. Nadel finds quantitative differences in the excretion of three steroid hormones by leukemic guinea pigs. Similar changes are being sought in patients by Dr. Nadel and Dr. Emil Frei, III. The principal corticoids excreted by guinea pigs depend upon the genetic constitution of the subjects. Radioactive acetate is incorporated in increased amount into cortisol and corticosterone by adrenals of scorbutic guinea pigs, and each of these steroids has been identified in their other tissues by Dr. Nadel and Dr. Shlomo Burstein (Visiting Scientist).

Dr. Max Sherer's observation that steroid hormones influenced the levels of circulating protein bound iodine has led to a study of compound released by the thyroid gland stimulated by those hormones. No qualitative changes have been found. Dr. Sherer, Dr. Harold Altman, Mrs. B. N. Siefring and Dr. Paul Marks (NIAMD) have found a lower level of protein bound iodine in blood from hepatic veins than in arterial or other venous blood. This has permitted calculation of the quantity of protein bound iodine removed by the liver, thereby providing the first measure of entero-hepatic circulation of thyroxine in man.

Studies of the mechanisms by which thyroid tissue accumulates iodide are important to a better understanding of many aspects of thyroid cancer. Dr. Seymour Wollman and Dr. R. O. Scow (NIAMD) find that iodide and thiocyanate compete for the same sites for forming complexes in the thyroid. The affinity for iodide is twice that of thiocyanate even though some drugs containing the latter radical are capable of producing goiter and even thyroid cancer. Thiocyanate is not concentrated by the thyroid as is iodide and the mechanics of thiocyanate action apparently involve active transport rather than simple adsorption.

Protein Chemistry and Metabolism

Substantial advances in technology resulting from efforts of the staff of the Laboratory of Biochemistry, NCI, have permitted more rapid progress in this field concerned with the synthesis, characterization and reactions of the most abundant non-aqueous constituent of protoplasm responsible in large measure for cell growth and function. The approach to study of proteins includes precise studies of their precursors; amino acids and peptides.

Amino acids and peptides: Constant improvements are being made in the production of pure, optically active amino acids. Drs. R. D. Marshall (Visiting Scientsit), S. M. Birnbaum and J. P. Greenstein find cobalt ions helpful in hydrolyzing the more resistant forms of acylamino acids. A new form of acylase more active against certain substrates is prepared by incubating standard preparations with cobalt acetate and dialyzing away the unbound material.

Drs. Milton Winitz, J. P. Greenstein, S. M. Birnbaum and Mr. R. J. Koegel have used measurements of optical rotation and rotatory dispersions to determine the optical configuration of the beta-asymmetric center of isoleucine. Some enzyme systems apparently demonstrate a rather marked and characteristic response to substrates with a beta configuration, whereas others exhibit a more random and sometimes indifferent response; in other words, some enzymes are highly exacting and some are capricious in their requirements.

Extensive studies on the metabolism of amino acids and related compounds by the intact rat have yielded rather unexpected results. Dr. Greenstein and his associates determined the lethal toxicity of each of the 10 essential amino acids in terms of quantity required via intraperitoneal injection to kill 50 and 99.9 percent of the subjects. The lethal toxicity of isoleucine, valine, leucine, phenylalanine, methionine, threonine, histidine, lycine, arginine and tryptophan increased in that order. D-isomers were equally or less toxic than the corresponding L isomers. Some of these amino acids caused marked decreases in blood sugar; lysine, however, significantly increased concentration of blood sugar, while threonine had no effect.

Mixtures of the 10 L amino acids possessed a toxicity less than that calculated from the sum of the arithmetical means of their individual toxicities. One compound of this mixture was removed at a time and the toxicity of the resulting 9 mixtures compared. In only one case was agreement good between observed and calculated toxicity -- the mixture in which arginine was lacking. It appeared, therefore, that arginine exerted some protective effect against the toxicity of the other amino acids. This was proved by adding L-arginine in varying amounts to a mixture of the other 9 amino acids and observing a reduction from 100 percent mortality to

24 percent with extremely small concentrations of L-arginine.

Additional experiments clearly incriminate ammonia or ammonium ion production in the toxicity of argine-less amino acid mixtures. In all probability a surfeit of amino acids in body fluids is metabolized by deamination, conversion of the amino group to urea and combustion of the carbon residues via the usual pathways of carbohydrate metabolism. Arginine is known to be an important compound in the production of urea according to the scheme described by Krebs and Hensleit. Dr. Greenstein and his co-workers were able to prevent lethal toxicity of ammonium acetate by treatment with arginine. A large number of related compounds were explored, but protection was afforded only by those which permitted conversion of ammonia to urea. Parallel work by Dr. J. L. Fahey in dogs proved the toxicity of arginine-less amino acid mixtures for canine species and revealed an increase in blood ammonia associated with the toxic symptoms, both of which were reversed by arginine administration. The total experience clarifies a long-standing controversy on the necessity of arginine as a nutrient.

In addition to providing mixtures of pure, optically active amino acids for parenteral administration to patients who cannot eat, Drs. Greenstein, Winitz and Birnbaum have compounded a completely synthetic, water-soluble diet that permits good growth in rats. The adequacy of this regimen as a complete diet for man is being evaluated.

Peptides are intermediate between amino acids and proteins, being composed wholly of amino acids. Some reason exists to suspect that proteins may be formed both from amino acids, as such, or as peptides, hence the characteristics and reactions of these important molecules are noteworthy. Mr. Koegel and his colleagues, studying solid state infra-red spectra of 93 peptides containing only 2 amino acids each, find shifts in absorption maxima due to such groups as methyl, ethyl, terminal carboxyl and amide. The internal structural units in such complex molecules absorb as they do in simple, straight chain paraffins, thereby providing a useful basis on which to approach their identification.

Work on isolation and characterization of peptides in human urine is already in progress. Dr. C. G. Baker and Dr. T. B. Moore (Research Fellow) find good agreement between calculated and observed Rf values for 75 synthetic peptides in 15 solvent systems. High salt concentration proves a serious obstacle to isolation of peptides from body fluids, but Drs. Baker and Moore have tentatively identified 7 such compounds. Glutamine, asparagine and glycine are the amino acids represented most often in the peptides already isolated.

New and important chemical reactions of the peptide l-cysteinyl-L-cysteine are described by Drs. Greenstein, Winitz and Roy Wade. The products of oxidation are sensitive to changes in hydrogen ion concentration and include a hitherto undescribed cyclic monopeptide.

Proteins: Methods originated by Drs. H. A. Sober and E. A. Peterson for the separation of undenatured soluble proteins have been developed further by defining procedures for evaluating adsorbents which already provide for more rapid separation using smaller quantities of protein mixtures. Some of the adsorbents originally described by these scientists are being produced commercially, good evidence of the high importance in which their contributions are held by the chemical profession. Drs. Peterson and Sober have fractionated human blood serum to yield the colored protein siderophyllin, methemealbumin, ceruloplasm and colorless glucosamine, orosomucoid and thrombin. Rapid short column procedures segregate proteins into groups with similar properties. Dr. Jacques Oudin (Pasteur Institute, Paris, France) has materially aided NCI investigators, while serving as a visiting scientist, by application of his precise immunologic techniques to the isolation and characterization of other colorless proteins. Serum albumin is separable into at least three electrophoretically distinct entities which, unfortunately, possess such close antigenic properties that immunologic techniques cannot discriminate among them. This need not be the case with other proteins, and search for biological properties requires other than physico-chemical means of identifying the proteins of tissues and body fluids.

Chromatographic techniques have permitted purification of additional enzymes with good recovery. New activities and substrate specificities have been found. Drs. Peterson and Sober are able to separate electrophoretically homogeneous hemoglobin into chromatographically distinct entities. Dr. H. R. Itano has described an additional, 8th, inherited abnormal hemoglobin termed "J" but its relation to disease states is unknown at this time.

The continued growth of cancer in the human body alters the distribution of plasma proteins, ultimately reducing their concentration seriously when the lesion becomes advanced and disseminated. Reduction in concentration of serum albumin is often pronounced. These phenomena, though established by many workers, have never been explained satisfactorily. The entire subject of plasma protein abnormalities is being studied by Drs. J. L. Fahey, J. L. Steinfeld, D. M. Watkin, H. A. Sober, and E. A. Peterson. It is possible that the decrease in albumin is more apparent than real, reflecting primarily an increase in plasma volume and marked overproduction of globulins. Data in the medical literature do indicate an expanded plasma volume in some cancerous subjects though others have found normal values. Dr. Steinfeld has measured plasma volume by using albumin labeled with radioactive iodine (I^{131}). The total circulating red blood cell mass was determined independently with radioactive chromium (Cr^{51}). No major increase in plasma volume was revealed and, indeed, recalculation of conflicting data published by others permits reconciliation of the divergent views. The possibility of increased utilization of serum albumin was also recognized but Dr. Steinfeld reports a significant decrease in total exchangeable albumin in advanced cancer with decreased or low normal turnover

rates of albumin. Hypoalbuminemia in cancerous patients would not appear to be due to failure of albumin production in the sense that it cannot keep pace with utilization.

Enzymes: Enzymes are proteins which catalyze important biochemical reactions. Treatment of rats with isonicotinic hydrazide, a drug useful in management of tuberculosis, results in diminished transaminase activity, according to Dr. Alton Meister. These enzymes permit shifting of amino groups between amino acids and alpha keto acids, important intermediates in carbohydrate and protein metabolism. The reduced activity of the transaminases can be restored in vitro by addition of pyridoxal phosphate or pyridoxamine phosphate. Probably isonicotinic hydrazide interferes with activity of the coenzymes needed for transaminase activity.

Dr. Meister has also explored transamination as an important factor in production of phenylpyruvic oligophrenia, a rare disease of infants characterized by mental defect and greatly heightened excretion of phenylpyruvic acid and phenylketone bodies in the urine. Administration of glutamine or asparagine decreases the output both of phenylpyruvic and phenyl lactic acids. These findings suggest that the excessive amount of phenylpyruvic acid is formed by transamination and, further, that limiting the intake of phenylalanine with concomitant treatment by glutamine may benefit these patients.

Dr. Leon Levintow and Dr. Meister describe a highly purified enzyme catalyzing the synthesis of glutamine from glutamic acid, adenosinetriphosphate and ammonia. Glutamine synthesis and glutamyl transfer both are catalyzed by this same monodisperse enzyme. The glutamyl transfer is not reversible, which leads to the conclusion that this enzyme catalyzes both the synthesis of an amide bound and a transpeptidation reaction.

Investigations of the mechanisms by which the activity of hepatic catalase is reduced as the result of cancerous growth elsewhere in the body have led to a general study of iron metabolism in tumor-bearing subjects. Real progress is being made by Drs. V. E. Price and R. E. Greenfield. Claims of Nakagawa that urine fractions reduce hepatic catalase activity in the experimental subject have been substantiated by Mr. W. R. Sterling, Dr. Price and Dr. Greenfield, though the degree of inhibition is somewhat less than observed by the Japanese investigator. The urine extracts from normal subjects exhibit less total activity than do extracts of urine from cancerous subjects but the potencies are equal in terms of inhibition produced per unit weight of extract injected.

A number of proteins contain iron, usually in the form of heme, an insoluble, non-protein protoporphyrin associated with respiratory enzymes and pigments. Catalase, hemoglobin, cytochromes all contain iron. The greatest single store of iron in the healthy animal appears to be in the liver, but Drs. Price and Greenfield have

found that relatively large tumors in rats contain more iron than is stored in their livers. These rats are commonly anemic and the life expectancy of their red blood cells is dramatically reduced. If red blood cells from healthy rats be labeled with radioactive iron (Fe^{59}) and transferred into the tumor-bearing animals a large proportion of the radioactivity becomes sequestered in the cancerous tissue. The same result is obtained with red blood cells tagged with radioactive chromium (Cr^{51}) even though this label be distributed somewhat differently in the erythrocyte. Dissolution of the labeled red blood cells yields labeled hemoglobin and erythrocyte stroma. Injection of the lysed product into tumor-bearers results in concentration of radioactivity in the liver and excretion of a large fraction in the urine, providing strong evidence that cancerous tissue achieves its large stores from red blood cells without major disruption of their structure comparable to that of in vitro hemolysis. The rate at which Fe^{59} is cleared from labeled plasma and incorporated into red blood cells is a good measure of red blood cell formation. Drs. Greenfield and Price find the uptake of plasma labeled with Fe^{59} enters tumor more readily than does the label from red blood cells but, in addition, the rate of incorporation of Fe^{59} into erythrocytes is increased in the cancerous as compared to the healthy subject. These studies, then, have reproduced the situation found in some proportion of cancer patients -- anemia, shortened life of red blood cells but increased rate of red blood cell formation -- as originally described by Ross (Boston University). Drs. Greenfield and Price have focused attention on the role of a pathological tissue in demanding an inordinately larger proportion of the limited stores of iron-containing materials available to the cancerous host in producing deleterious situations inimical to its survival. This problem is also being approached in clinical investigations. Dr. J. L. Steinfeld reports varying degrees of reduction in red blood cell survival among 18 anemic cancerous patients studied by him, using isotopic procedures. The total circulating red blood cell mass is consistently decreased in 80 studies of 60 patients with advanced cancers.

Nuclic Acids

Nucleic acids are large molecules made up of many smaller units such as purines, pyrimidines, 5-carbon sugars and phosphorus. Intermediate between the small molecules and the gigantic nucleic acids are comparatively simple phosphorylated structures, ribotides and ribosides. Nucleic acid research in its broader sense assumes increasing importance on an international scale because:

1. Nucleic acids are thought to be closely associated with genic material responsible in large degree for individuality among species and even among cells.

2. Some therapeutically effective anticancer agents are thought to act through interference with production of nucleic acids. Some believe that the biological characteristics of cancer cells are due

to a fundamental difference between the nucleic acid composition of normal and cancerous units. Dr. W. C. Schneider is principally concerned at this time with determining the quality of pyrimidine deoxyribosides in normal livers and in tumors derived from the cells of the liver responsible for its major functions. Deoxycytidine accounts for essentially the entire deoxyribosidic activity of the healthy rat liver. In contrast, extracts of the Novikoff hepatoma show 3 striking differences in the types of deoxyribosidic compounds they contain:

1. The deoxyriboside fraction accounts for only 50 percent of the total microbiological activity used in measuring these compounds.

2. Thymidine and deoxyuridine are present as well as deoxycytidine.

3. The compounds responsible for the remaining activity have not yet been identified.

Studies of regenerating rat liver reveal that the total amount of deoxyribosidic compounds present is approximately doubled as early as 24 hours after partial hepatectomy, and, in contrast to normal liver, 25 to 50 percent of the total deoxyribosidic compounds appear in the unidentified fraction. The stimulus to multiply, as exemplified by the rapidly growing regenerating liver, obviously changes the chemical composition of the organ. Additional work is required before the attributes of the hepatoma may be selectively defined.

Cytochemical studies also point up differences in distribution of nucleic acids relating to functional state of cells. Drs. E. L. Kuff, G. H. Hogeboom and A. J. Dalton are working with a new method devised by them for cellular fractionation. Three types of particles are obtained from rat liver: mitochondria, a group demonstrating acid phosphatase and uricase activity, probably associated with ergastoplasm, and a group of particles that may be related to the Golgi apparatus. Ribosenucleic acids are present in all fractions in ratios of 10, 30 and 50 percent, the remainder being non-sedimentable in 30 percent sucrose. During rapid growth that follows partial excision of the liver, ribosenucleic acid, largely residing in non-sedimentable fraction, disappears from the particulate group possessing high acid phosphatase activity.

Further characterization of nucleic acids is highly desirable. Dr. Joseph Shack is employing an analytical approach to the study of deoxyribonucleic acid and its fractions produced by comparatively gentle chemical manipulations. The ultraviolet absorption spectra of native deoxyribonucleic acids are constant over a wide range of temperatures and salt concentrations, but marked variations followed modifications of the original compounds. Additional enzymes degrading deoxyribonucleic acid have been found.

Dr. Herbert Kahler, Dr. Shack and Mr. B. J. Lloyd find a higher sedimentation velocity and greater boundary spreading of deoxyribonucleic acids in solutions containing bivalent ions as compared to solutions of monovalent ions.

Morphological studies: No essential qualitative difference has been found by Dr. A. J. Dalton and Miss M. D. Felix between normal and neoplastic cells examined by electron microscopy. Increasing degrees of dedifferentiation among cancer cells are accompanied by a tendency for small granules to lie free in the cytoplasm rather than to be oriented along the membranous network of the ergastoplasm, and large vacuoles disappear from the Golgi apparatus.

A television microscope designed and constructed by Dr. G. Z. Williams permits analysis of absorption spectra of cells exposed to monochromatic ultraviolet light. Consistent differences are noted by Dr. Williams between the ultraviolet absorption maxima of nuclei from normal cells and cells obtained from mouse ascites tumors. Hematoporphyrins absorb strongly at 410 mu, permitting the accurate recognition of early progenitors of red blood cells which in general structure closely resemble the more primitive precursors of the white blood cell series. This work assumes an immediate practical utility.

Surgically created polypoid projections of the mucous membrane lining the stomach of the dog led to atrophic changes in the elevated mucosa, as reported by Dr. M. K. Barrett.

Using histochemical techniques for studying distribution of succinic dehydrogenase, Dr. Emma Shelton finds increased activity of the enzyme in very small hepatomas produced with o-aminoazotoluene. The tetrazolium method for succinic acid dehydrogenase measurement is less sensitive than other techniques which do not lend themselves to topographical studies, but the ratios of activity seem to be comparable in both cases.

Dr. W. G. Banfield has developed methods for discriminating between the young and old collagens in tendons and scars. Young collagen as typified by recent scars contains large amounts of acid-soluble material which disappears as the scar ages. The properties of these major connective tissue proteins are important since some cancers spread through apparent dissolution of collagenous matrix, while others are restrained by apparently identical material. The techniques originated by Dr. Banfield may permit more detailed study of invasive properties of cancer cells in their normal location.

Studies of factors concerned in development of adult type structure consequent on embryonal growth and differentiation have been primarily concerned with the metanephric kidney mesenchyme during the past year. This rudiment never forms tubules when isolated by itself in tissue culture by Dr. Clifford Grobstein observes tubule formation when the mesenchyme is transplanted into the adult eye or brain, even though tissue from these sources demonstrate no morphogenetic capacity in vitro.

Malignant melanomas are thought to arise from nevi, commonly called moles. A considerable proportion of the malignant tumors arise on the soles. Dr. E. J. Van Scott and associates have examined more

than 700 individuals of whom about 25 percent have pigmented lesions on the palms or soles. Most of the lesions biopsied prove to be junctional nevi which seem particularly prone to the development of cancerous change. A proposal to prevent development of malignant melanoma on the palms and soles by excision of all pigmented lesions on those surfaces would require subjecting a very large fraction of the population to surgery and would fail to include barely discernible nonpigmented lesions with equally serious potentialities.

Immunologic studies: A number of investigators from different laboratories have reported the apparent production if isologous immunity to sarcomas induced by methylcholanthrene. Isologous immunity refers to immune mechanisms operating in a single individual or in genetically homogeneous groups in which the members are as alike as identical twins. Since it is the prevailing opinion that neoplasms are non-antigenic in the animal or strain of origin, the results reported by these investigators have been attributed to probable unrealized genetic heterogeneity of the experimental subjects. Dr. R. T. Prehn, however, has shown conclusively that isologous immunity can be demonstrated regularly among sarcomas produced by methylcholanthrene, but no such phenomenon can be shown with "spontaneous" sarcomas or mammary carcinomas. Dr. Prehn proposes as alternative explanations the possibilities that the isologous immunity is due to small residual heterogeneity which would not account for the failure of "spontaneous" neoplasms to exhibit similar properties or some more fundamental difference between the tumors produced by the chemical and those occurring without known chemical stimulus. Fortunately, experimental means are available for discriminating between these hypotheses.

HeLa Cells, originally obtained from a woman with carcinoma of the uterine cervix, will grow in diffusion chambers placed in the abdominal cavity of a mouse when the porosity of the chamber walls prevent access of host cells. Dr. G. H. Algire reports the occurrence of degenerative changes on continued residence, but some cells appear healthy as long as 50 days after transplantation. HeLa cells grown in hosts that have previously been immunized against that particular cell line are destroyed within one week, apparently by antibodies that cross the membranes of the diffusion chamber.

Metabolic studies: Physical deterioration of the cancerous host occurs frequently both in the clinic and laboratory, the reasons for which have not been satisfactorily defined. Evidence presented in recent years has incriminated disturbances in energy metabolism as an important factor in weight loss. New experiments conducted by Dr. A. W. Pratt, Mr. W. C. White and Miss F. K. Putney bear importantly on this subject. Their experiments involve the precise, continuous measurement of oxygen consumption and carbon dioxide elimination, by electronic devices, of rats bearing a transplanted tumor. Transplantation is followed by a transitory rise during the few succeeding days, which antedates appearance of the growing neoplasm.

The reason for this phenomenon is not clear. Continued growth of the tumor is accompanied by a gradual but steady increase in oxygen consumption, and the production of carbon dioxide tends to fall. The resultant decrease in respiratory quotient may be due to increased utilization of fats as fuels. These observations cover only the period preceding onset of appetite loss and clearly suggest a heightened expenditure of energy during that period. The excessive energy production is derived almost entirely from non-protein sources even when caloric expenditure exceeds caloric intake. The increasing energy expenditure of the cancerous host should play a major role in production of weight loss and would become particularly important if loss of appetite, restricting the subject's intake of fuels, were not accompanied by a decrease in metabolic rate. The healthy human reduces his metabolic activities when the dietary intake is maintained at 1500 calories per day, as shown in the Minnesota experiment, but increased basal metabolic rate is reported frequently among cancerous subjects, particularly those with advanced disseminated disease. The basic problem will be explored further in model systems with a view to approaching critically important points in the clinic. At this time, however, loss of appetite, extremely frequent among cancer patients, assumes major importance.

Little is known about the control of appetite, but deletion from the diet of any essential nutrient which the body cannot manufacture seems to be followed within a comparatively short time by rejection of that diet by experimental animals. Possibly the growing cancer incorporates inordinate amounts of some important compound in its substance and by virtue of its continuing growth effectively robs the body of an essential metabolite. Support for this contention is afforded by the experience of Dr. Julius White in maintaining appetite among rats bearing an experimental neoplasm by incorporating tumor itself into the diet. A good diet in which casein is the only source of protein is accepted readily by healthy rats but the cancerous subject ultimately rejects it, loses weight and dies. An isocaloric diet in which tumor provides the only source of protein is accepted readily by both normal and cancerous rats. The tumor bearer does not lose weight, eats well throughout the course of cancerous growth and has an extremely short period of terminal morbidity. Comparable healthy or cancerous rats ingesting the two diets excrete almost identical total amounts of nitrogen but the ratios among the nitrogenous compounds in the urine are quite different. Efforts are directed toward identification of the dietary ingredients responsible for prevention of weight loss and maintenance of appetite.

The concept that a tumor may hoard materials important to the host's economy was developed above in the discussion of work reported by Drs. Price and Greenfield. Additional supporting evidence is provided by Dr. J. C. Reid, who fed the amino acid glycine labeled with radioactive carbon (C^{14}) to rats bearing small tumors. The isotope could be found in the neoplasm one hour after administration and substantial activity was present 4 days later. Continued growth of the

cancer results in a radio-autograph showing a central core containing radioactive material surrounded by a rind of cancerous tissue with extremely little C^{14}. The greatest isotope concentration occurs in an area roughly corresponding to the profile of the tumor at the time the radioactive glycine was fed. Normal organs and tissues are thought to be in a dynamic state of equilibrium whereby their structural components are in a constant process of being formed, broken down and replaced. The preliminary observations of Dr. Reid suggest that this situation may not apply in the case of some cancers. The concept is not entirely new, but the relevant work already accomplished by NCI scientists indicates a fruitful field for further study.

Dr. Herbert Kahler's observation of an acid reaction among tumors following administration of glucose has been extended to a wide variety of cancers, hence appears to be a valid generalization. During the past year, Dr. Kahler has found that acidity varies within a given tumor in a reproducible fashion, suggesting some differences in metabolic activity associated with topographical situations.

THERAPEUTIC RESEARCH

The program of NCI attempts to improve surgical and radiological approaches that have dealt effectively with some cancers over the years and, in addition, develop agents which may be given systemically to cure disseminated cancers. The long range objective - therapeutic control of cancer in man - required basic research in many different types, including a substantial proportion of the work previsouly described and analysis of biochemical and physiological deficits incurred by cancerous patients.

Surgery

Additional experience with the seeding of operative wounds by cancer cells indicates a much greater than anticipated frequency of contamination. The local recurrence rate, though already high, should by logical reasoning be higher, and variability in duration of apparent health that precedes recurrence is striking. The brilliant achievements of Dr. R. R. Smith and Dr. A. W. Hilberg in defining this extremely important problem should be exploited by obtaining a far longer experience. This cannot be obtained at NCI where patients are referred only after diagnosis has been established. It requires a hospital of the type which accepts larger numbers of patients so that a random experience may be studied. Aside from the purely pragmatic aspects of the research one may confidently expect to learn a great deal about certain biological attributes of clinical cancers which are not likely to be found from study of laboratory animals alone.

Dr. Smith and his associates have devised animal systems in which the problem of sterilizing contaminated wounds can be investigated. The models reproduce faithfully the clinical situation. Washing with physiological saline alone decreases the number of cells that grow but does not sterilize the wounds. Some drugs cause general toxicity when used in the wash fluid. A 1 percent solution of formaldehyde is the best agent yet discovered, but changing the hydrogen ion concentration in the wounds by appropriate buffer solutions shows considerable promise. Dr. Smith and co-workers, studying the ability of experimental neoplasms to establish new deposits in the lungs following intravenous injections of cells, find that the number of pulmonary lesions caused by the S91 melanoma may be doubled by many different stressful situations. Colleagues in the Laboratory of Chemical Pharmacology have been most helpful in providing agents used by members of the Surgery Branch in this work.

Further experience with radical surgery as a means of definitive treatment in cancers of the paranasal sinuses has been obtained. Extension of cancer to the middle cranial fossa proves to be a serious limiting factor in operability. This type of spread does not necessarily produce any recognizable symptom complex, nor can precise roentgenologic techniques detect involvement prior to erosion of the cranial bones.

Radical operations for cancers of the uterine cervix have been performed with operative mortality of less than 4 percent. The surgical procedures have included complete pelvic exenteration, or radical hysterectomy with excision of the regional lymph nodes, and one radical resection of a carcinomatous stump developing after earlier supravaginal hysterectomy. The immediate results have been generally gratifying but it is much too early to evaluate long term effects of these procedures.

Dr. W. E. Schatten has devised an operation for reconstruction of the common bile duct. He has used split thickness skin grafts successfully in 14 of 17 dogs. A longer period of observation is required before the procedure may be tried in man since the possibility of late stricture development cannot be eliminated yet.

Ionizing Radiations

The program of the NCI in radiation research includes studies necessary to provide better means of treating cancers with ionizing radiations from machine-generated and isotopic sources and approaches to the therapeutic problems posed by potential exposure of large numbers of the population to atomic detonations. Both types of program require many basic experiments which are included in this section for the sake of convenience.

Therapeutic efficacy of X-rays is largely based on relative susceptibility of normal and neoplastic cells to ionizing radiations. It is in all probability a quantitative rather than a qualitative difference which may be exploited only when the relative susceptibilities are of a practical order of magnitude. Fractionation of X-ray dosage as practiced by Coutard permits the more rapid recovery of healthy tissues, hence, less undesirable side reaction for a given therapeutic dose and even a greater total dose to the neoplasms. Familiarity with increasing total doses of X-rays delivered over periods of 30 days or less suggests the possibility that the total dose may be increased without producing serious damage to normal structures by giving small fractions over an even longer period of time. Dr. J. R. Andrews is testing that hypothesis. Very preliminary results are encouraging. The first few cancer patients so treated have had immediately favorable tumor responses with barely detectable reactions in the overlying or adjacent tissues. Scarcity of suitable patients for this program impedes progress.

Occasions arise when cancers are so disseminated that treatment of every affected area with X-rays is tantamount to total body irradiation. The effectiveness of X-ray therapy is seriously reduced because of the limitations on dosage imposed by such circumstances. Mycosis fungoides, an uncommon type of neoplasm related to lymphomas, is generally widely distributed in the skin. It is sensitive to machine-generated X-rays to some extent, but radiations of this type have great penetrating power. Dr. J. R. Andrews, following the lead of radiologists at the Massachusetts Institute of Technology, is exploring the effectiveness of electron beams generated by 2 MEV electrostatic generators in treating this condition. The electrons penetrate no more than 5 mm. into the skin and have a therapeutic effect comparable to conventional X-rays. Healing that follows either type of treatment is associated with the production of fibrous tissue which converts the normally pliable skin into a semi-rigid covering causing distress to the affected patients. This undesirable consequence would seem to be a serious limiting factor in advocating widespread use of electron beam therapy as a major advance in the treatment of mycosis fungoides. The treatment of other supervicially located cancers with electrons is being explored.

Study of experimental tumors provides means of developing new methods of using X-ray therapy in patients. Mrs. Joanne Hoffcroft finds no increase in radiosensitivity of mouse lymphoma #1 following procedures that alter the blood supply of that particular tumor. Combined treatment with cortisone and X-rays produces additive effects. The combination of certain anticancer drugs and X-rays produces responses that vary according to the intervals between administration of each agent. The same rate of regression is obtained when a constant dose of X-irradiation is given daily or in 4 equal fractions at intervals of 2 hours. Less effect is obtained when

doses are spaced 2 days apart.

Another lymphoma, #2, studies by Mrs. Hoffcroft, seems to be more sensitive to X-rays when treated in the host than when the same amount of irradiation is delivered to the neoplasm irradiated in vitro. The same type of observation obtained from the study of other neoplasms may indicate some indirect effects of X-rays on cancer that are yet to be defined. Another interesting experiment with mouse lymphoma #2 permits study of X-ray effects on disseminated cancer. Mrs. Hollcroft transplants bits of liver and spleen which ordinarily give rise to new lymphomas in the recipient host following transplantation. Few of the transplants grow when taken at once or 4 hours after treatment, but increased viability is noted thereafter.

Additional pertinent information is afforded by studies of X-ray effects on the small intestines of rats reported by Dr. J. White and Dr. R. B. Williams (NNMC). X-irradiation retards synthesis of deoxyribonucleic acid and proteins. Three days later synthesis is increased concomitant with cellular division. Divided doses are more effective in permitting recovery than is a single dose of the same total magnitude. The individual dose and the time interval between divided doses are important. The smaller the interval between doses the greater the damage.

Among important factors that may retard the growth of X-irradiated cancers are effects on their blood supply. Dr. R. M. Merwin finds that a dose of 2000 r prevents the formation of capillary sprouts in response to injury. The effect may last as long as a year, probably because the total blood supply of the exposed part is markedly reduced. Earlier experiments by Dr. H. S. Kaplan and Dr. Merwin showed disappearance of the afferent blood vessels feeding the tumor, with reestablishment of circulation by ingrowth of new vessels from the unirradiated area.

Precise dosimetry is essential to good radiotherapy. Ingenious systems have been devised to permit physical measurements in phantoms but none is completely satisfactory. Development of a novel method showing great promise for improving the situation with respect to high energy X-rays is reported by Dr. H. L. Andrews. He finds it practical to exploit known chemical reactions induced by ionizing radiations such as the production of hydrochloric acid from chloral hydrate and the oxidation of ferrous iron to the ferric state. The reactant chemicals are incorporated in a gel which makes it possible to see the beam of radiant energy and to measure changes in the medium with a probing electrode.

The experimental 3 MEV Van de Graaff electrostatic generator, gift of the Liggett and Myers Tobacco Company, is a valuable machine but melts gold targets when operated at one-quarter of its rated capacity. Intensities higher than this are sorely needed in biological work. Dr. H. L. Andrews has explored the matter satisfactorily,

finding that the highest possible voltage will give increased output for the same degree of target heating. All target failures, to date, seem to be due to a burst of high current lasting for about 1 microsecond. Dr. Andrews proposes to reduce local heating by providing a sweeping incident beam over the target at a very high speed.

Total body irradiation of rats results in a sharp change in survival from 5 days to 24 hours when the dose equals or exceeds 6000 r. Death is associated with marked signs of increased central nervous system irritability, according to Drs. H. L. Andrews and K. C. Brace. These investigators correlate the central nervous system signs with pathologic changes in the granular cells of the cerebellum occurring within 1 hour after exposure. About 90 percent of the cells are affected within 8 hours and neurologic signs are closely related to the amount of cellular degeneration. Dr. Andrews and Brace report a striking effect of administration of barbiurates prior to irradiation with doses as large as 15,000 r since barbiturate treatment produces a picture similar to that seen below 5,000 r with survival of 4 days.

Although transplantation of bone marrow or treatment with spleen homogenate protects mice against acute death from total body irradiation these procedures do not necessarily abolish all consequences of the exposure. Dr. Falconer Smith reports damage to immune responses as measured by sheep hemolysis titers. Irradiated mice seem to be generally more susceptible to specific antigens to which they have been sensitized than are non-irradiated mice.

Dr. W. W. Smith has extended studies of total body irradiation to hamsters. Among those which survive for one month, the median survival time is directly related to the dose of X-rays rather than to the proportion of those surviving the first month. Treatment with streptomycin or bone marrow prevents early death without promoting complete recovery. Pathologic studies of Dr. Smith's material by Drs. George Brecher (NIAMD), K. C. Snell and R. L. Swarm reveal high incidences of gastric ulceration, pneumonia, vascular and renal changes and neoplasms depending on the initial does of X-ray and survival time.

Dr. C. R. Maxwell has elaborated further details of the chemical events that follow X-irradiation of glycine solutions in terms of production of free radicals. Failure to find formaldehyde among the products as the result of free hydroxyl ions leads to the conclusion that the reaction is limited to high local concentrations of free radicals. Reductive deamination leads to acetic acid production and oxidative deamination produces glyoxalic acid. Alpha particles from polonium (Po^{210}) induce the same changes as X-rays or electrons on glycine solutions but ratios of the end-products differ and formaldehyde is formed. This type of study may, in time, lead to a definitive investigation of biochemical reactions initiated in tissues

by ionizing radiations. The infinitely greater complexity of protoplasm requires the study of comparatively simple model systems as a means of guiding the ultimate biochemical approach.

Other forms of radiant energy than ionizing radiations have important effects in biology and medicine. Dr. M. M. Elkind is studying variables controlling sensitivity of yeast cells radiated with visible light. Sensitivity is measured by colony growth and is related to changes in pH, duration in storage, environmental temperature and oxygen tension. Early results indicate that actively proliferating cells develop sensitivity more readily than do resting ones.

Endocrinological Approaches

Steroid hormones: These were the first class of compounds which altered the course of specific anatomical types of cancers when administered systemically. Steady progress in defining limitations of hormone therapy has developed the concept that some neoplasms require one or another hormone for their anatomical and functional integrity just as do the normal cells in the organs from which the cancers arose. Escape from endocrine control is an all too common pattern. The relative importance of evolutionary changes in the cancerous units themselves or in the metabolic alterations in their hosts has not been satisfactorily delineated but the total experience in endocrinological aspects of cancer research clearly emphasizes the need for fundamental research in the basic role of endocrines in the growth and development of normal organs and tissues.

Cancers of the breast are influenced by treatment with male (androgen) and female (estrogen) sex hormones. Experience with 218 patients suffering from mammary carcinoma has been accumulated by Dr. Roy Hertz over the years. His use of relatively massive estrogen therapy permits definition of necessary precautions. Variations in the course of mammary cancers and in responses to massive estrogen therapy make precise analysis of results most difficult, but clinical impressions suggest certain advantages over conventional daily administration of relatively small doses of estrogenic substance. Vaginal bleeding occurs in about 15 percent of women with breast cancer on cessation of estrogen therapy but is a constant occurrence in patients less than 40 years old. Some additional factor other than estrogen must be essential for activation of the human endometrium else the sharp distinction between age groups would not be evident.

Dr. Hertz, with Drs. D. M. Bergenstal and M. C. Li, are disappointed with the results of intravenous androgen therapy and have suspended further study. The patients' tolerance is not good and hormonal activity cannot be detected in the blood stream. Serious difficulties have been encountered in preparing satisfactory solutions for

intravenous use. A new androgen, 17 ethyl-19-nor-progesterone, known to favor the storage of nitrogen, seems to present no marked advantages over other already available androgens for treatment of cancers of the breast.

Removal of the ovaries has a beneficial influence on some patients with mammary cancers. Drs. Hertz, Bergenstal and Li have administered follicle-stimulating hormone from the pituitary to 6 women before oophorectomy. The expected stimulation of ovarian follicles was observed in most cases but no detectable rise in serum or urinary estrogen was noted nor could female sex hormone activity be found in blood from the ovarian vein. The situation, therefore, seems to be quite different from effects of pituitary adrenocorticotrophic hormone in producing readily detectable evidence of secretory activity by the adrenal cortex.

Drs. Hertz, Bergenstal and Li and Miss L. F. Hallman report exacerbation of carcinoma of the prostate by administration of chorionic gonadotrophin. This was not accompanied by increased excretion of estrogen or by appearance of detectable sex hormone activity of either type in spermatic vein blood.

Considerably more experience has been obtained with the clinical use of amphenone, a drug developed by Dr. Hertz which inhibits activity of the adrenal cortex. The endocrine activity of some adrenal cortical carcinomas and their metabolic effects on the host can be reduced unequivocally by this compound which seems to exert its greatest effect on the output of glucocorticoids. The number of observations is limited but the major aspects of the changes observed are quite reproducible. No objective influence on the growth of the adrenal cancers has yet been obtained. This is a critically important point. Some tumors which can not be seen or otherwise measured by physical techniques manifest themselves by peculiar pharmacologic effects resulting from their secretory activity. Identifiable and characteristic compounds are excreted by patients with such neoplasms. The excretory level may serve as a reasonable index of cancer activity, other things being equal. The ability of cancer cells to adapt themselves to changing circumstances has been suggested by experimental observations in laboratory animals. Continued experience with drugs that inhibit production of steriod hormones may be expected to shed considerable light on the possibility that even endocrinologically active tumors may dissociate their attributes of function and growth.

Amphenone is sedative to a pronounced degree. While it is extremely important, and to some extent useful, it might better be considered as a prototype compounds pointing the way to development of better agents. Dr. Hertz, Mr. W. W. Tullner, Jr., Mr. D. B. Spencer and Dr. D. M. Bergenstal are already working on new compounds. Some analogues of amphenone share its effects on the adrenal cortex in experimental animals, and further study of central nervous

system and general toxic effects are in order. Twenty-five related compounds are inert, though dichloro-diphenyl-dichloroethane (DDD) and Germanin are active. The latter material induced signs of adrenal cortical insufficiency when given to a patient with cancer of the breast. DDD and Germanin exert their effects by producing irreversible damage of adrenal cortical cells, whereas amphenone and its congeners interfere only with secretory activity, which is reestablished when drug administration ceases.

Transplantation of hormone-secreting tumors originating in the pancreatic islets, adrenal cortex or parathyroid glands to cortisonized rats was unsuccessful. Dr. Hertz and staff have differentiated the causes of sexual precocity in 5 more children during the year.

Cortisone benefits some cancer patients, especially those suffering from leukemias and allied diseases. The improvement, though real, is temporary. Dr. D. M. Watkin has examined prednisone, a relatively new drug with activity similar to that of cortisone. Prednisone proves to be more potent than cortisone but elicits numerous undesirable side effects when given in large doses. It is active against lymphomas, can induce changes in the plasma proteins in patients with multiple myeloma but cannot be recommended for treatment of the generality of cancer patients at this time.

Last year Drs. Dean Burk and M. W. Woods described an insulin-sensitive system concerned with glycolysis, the fermentation of flucose, thought to occupy a critical role in metabolism of cancerous cells. The ability of a given compound to inhibit insulin-sensitive glycolysis roughly parallels the capacity of that agent to induce necrosis, cell death, in an experimental tumor. Certain water soluble derivatives of podophyllotoxin, provided by members of the Laboratory of Chemical Pharmacology, inhibit anaerobic glycolysis in vitro of an experimental melanoma, and the effect is greatly enhanced by either male or female sex hormones. Combination of subminimal doses of a podophyllin fraction and diethylstilbestrol causes marked tumor destruction in vivo and, unfortunately, marked toxicity. Insulin, according to Dr. Paul Hochstein (Research Fellow) seems to play a key role in maintaining phosphorylating capacity of adenosine-triphosphate-deficient subcellular glycolytic systems involving the same hexokinase system that acts in the intact cell. The effects of estrogen on in vitro cellular metabolism described last year by Dr. K. M. Wight and Dr. Burk apply equally well at subcellular levels.

The discovery by staff members of the Laboratory of Biochemistry of the insulin-sensitive system concerned with glycolysis stemmed from observations of effects of stressful situations on the growth of some experimental cancers. Further exploration of additional tumors by Mr. J. C. Hunter, Dr. Woods and Dr. Burk indicates considerable variability in the response of different cancers to the common stress of

increased environmental temperature.

Necrotizing Agents

Search for new agents that damage cancers in the living animal continues. Dr. Morris Belkin and Associates completed preliminary observations on 100 agents obtained from Australian plants. Four percent of the agents were active against sarcoma 37. Drs. A.W. Schrecker and J. L. Hartwell completed stereo-chemical studies on podophyllotoxin polymorphism and isomerism necessary to establish correlations between chemical structure and tumor-damaging potency. Two materials of animal origin, both highly active in producing necrosis in tumors, are composed largely of nucleic acids.

Dr. D. L. Vivian's study of the vital dye, neutral red, indicates that it exists in 3 different forms, only one of which stains living cells. He has found a method which converts other non-staining phenazine dyes to true stains. A number of phenazines are known to produce damage in cancers, and Dr. Vivian's contribution may permit acquisition of important knowledge on their mechanisms of action.

Biological stains are continually being improved and their use extended. Dr. Belkin, for example, has studied the detailed sequence of events following introduction into the peritoneal cavity containing fluid syspensions of cancer cells ("ascites tumors") agents known to damage the same tumor growing as a solid mass. Certain polysaccharides cause direct damage with marked cytoplasmic vacuolation, cellular swelling and relatively little change in nucloi. Nitromin, a nitrogen mustard analogue, on the other hand decreases mitotic rate, increases the number of mitotic abnormalities and causes pronounced increase in cell volume. Precise definition of sequential changes resulting from drug action in this system may contribute a means of approaching important problems concerned with drug effects in solid neoplasms. Dr. Belkin has had to convert some cancers to growth in the peritoneal cavity. Of 16 hepatomas only 2 could adapt to this type of environment. Adaptation seems to be concerned with intrinsic growth rate rather than with degree of dedifferentiation (anaplasia).

The scope of research on biology and chemistry of polysaccharides has been increased during the year. Development of tolerance to a single injection of polysaccharide seriously limits its use in the treatment of cancer. Dr. M. K. O'Gara and Dr. Joseph Leiter were unable to confirm the presence of a factor in serum alleged to increase pyrogenicity of polysaccharides. They were able, however, to describe a change following incubation of polysaccharide with rabbit serum which influenced effect of the agent on tolerant and sensitive mice. Tolerant mice usually require 2 20-fold increase in dose to

produce 50 percent lethality and an even larger dose to influence tumors. Serum-incubated polysaccharide manifested a decreased toxicity without substantial change in the dose effective against tumors. The active agent in rabbit serum is thermolabile. Dr. D. P. Rall, studying incubated polysaccharides, found their pyrogenicity decreased but observed no effect on their ability to elicit the Shwartzman reaction or the histologically similar changes following intradermal injection of polysaccharides in some strains of mice.

Further experience with biochemical events associated with necrosis induced in neoplasms by necrotizing agents includes identification of additional enzymes concerned with carbohydrate metabolism which exhibit reduced activity. Evaluation of information currently available reveals evidence that decreased enzymic activity is not related to any particular association with subcellular structures. Disruption of tumor cells by physical means, such as ultrasonic vibrations, produces different changes in enzymic activity from that characteristic of drug action. These meticulous studies of Drs. V. S. Waravdekar and Joseph Leiter focus attention on the impairment of glucose metabolism as a major consequence of drug action. They reported earlier that diphosphopyridine nucleotide was also markedly reduced by nectorizing drugs. The normal rate of glucose utilization can indeed be reestablished in the damaged cancers by addition of this coenzyme. Additional studies indicate some interference with synthetic capacity on the part of the cancerous host since continuing growth of sarcoma 37 is accompanied by steadily decreasing activity of the synthesizing enzyme in a normal organ. This recalls the earlier work of Greenstein et al. on hepatic catalase. Injection of a tumor-necrotizing compound causes marked decrease in DPN formation in the tumor and an increased synthesis of the coenzyme in the liver.

Studies on diphosphopyridine nucleotide by Dr. Abraham Goldin and Dr. N. O. Kaplan (Johns Hopkins University) indicate enhanced synthesis of DPN in liver, spleen, kidney and neoplastic tissue after injection of nicotinamide, which can be reversed by the anticancer drug, 6-mercaptopurine. The drug action is partially antagonized by adenylic acid. Dr. Louis Shuster (visiting scientist) finds that isotopically labeled glucose is incorporated biosynthetically into DPN, more so into the mononucleotide moiety than into the adenylic acid portion. Thus, two different approaches to problems of cancer therapy are tending to converge. The antimetabolite principal so useful in conquest of bacterial infection grows ever more interesting as a potential weapon against neoplastic diseases.

Antileukemic Drugs

Striking remissions can be induced in the course of some acute leukemias with several different drugs which may be grouped together

as antimetabolites. The antifolic compounds are thought to interfere with the ability of folic acid or citrovorum factor to donate formate groups, small building blocks for the formation of larger molecules. The other class, exemplified by 6-mercaptopurine, presumably provides an altered compound which interferes with the function of the more complex molecules into which it is built. Both classes of drug are concerned with fabrication of nucleic acids. Many seem to think that blockage of nucleic acid synthesis is the primary mechanism concerned in the therapeutic effect even though other compounds are formed from formate or from purines. Animal experiments suggested trial of both drugs together as a means of obtaining a better and more lasting response. Experience of Dr. Emil Frei, III and his colleagues in treating a group of patients with concomitantly administered methotrexate and 6-mercaptopurine indicates no enhancement of therapeutic response.

Study of the fate of methotrexate in leukemia patients by Dr. C. G. Zubrod and Dr. M. V. Freeman shows rapid absorption and rapid excretion. If it should be desirable to maintain a constant concentration of the drug in circulating blood to achieve maximal benefit to the patient the dosage schedules employed in the past have probably not provided optimal circumstances for producing a measurable blood level. A relationship between blood concentration and therapeutic effect has not been shown in any chemotherapeutic research on neoplastic diseases and would seem to warrant intense investigation. The methods required to do this with methotrexate have been devised by Drs. Zubrod and Freeman. They have reason to believe, however, that the urine of patients treated with methotrexate contains more than one derivative. It will be necessary to identify these compounds and determine their biological effects as one of them may possibly be more important than methotrexate itself. This limited experience, however, has led to introduction of new dosage schedules into clinical trial.

Since methotrexate and aminopterin seem to interfere with the metabolism of folic acid and citrovorum factor it has been profitable to study the effects of the drugs on the fate and distribution of these compounds. Drs. P. T. Condit and David Grob (Johns Hopkins University) report clinical investigations suggesting that folic acid is readily taken up by the body's cells and subsequent utilization or conversion to citrovorum factor is an intracellular phenomenon. The system that utilizes folic acid can be overloaded by large doses of the vitamin. Administration of aminopterin inhibits utilization. Citrovorum factor is taken up by body cells more rapidly than is folic acid but the uptake is not influenced by aminopterin. Conversion of folic acid to citrovorum factor as indicated by urinary excretion is inhibited by drugs with anifolic activity.

Excretion of uric acid is often increased among leukemic patients and extraordinarily high concentrations of uric acid sometimes appear in the blood. The hyperuricemia has apparently been

increased in some cases by drug treatment to the extent that it, of itself, may constitute a serious problem in their management. The kidney is known to be intimately concerned with excretion of uric acid, hence the program now being developed by Dr. D. M. Watkin analyzes renal effects as contributing factors in the origin of hyperuricemia. It is already apparent that the uric acid problem is complex indeed since, other than the obvious role of the kidney, no single common denominator applies to each situation.

Laboratory experiments reported by Dr. Goldin, Mr. S. R. Humphreys and Mr. J. M. Venditti bear directly on clinical problems in leukemia therapy. The effectiveness of treatment, for example, proves to be influenced by the number of leukemia cells in the host. These scientists describe an approximately linear relationship between dosage of aminopterin necessary to save 50 percent of the recipient mice and the number of cells in the inoculum. An advanced transplantable murine leukemia is best treated with small, frequent doses of amethopterin in contrast to the larger, less frequently administered doses that are effective in earlier stages of the disease. Dr. Goldin and co-workers suggest that a dosage schedule effective in the advanced state provide minimum toxicity for maximal therapeutic effect. Additional studies indicate greater antileukemic action of aminopterin in older mice because such subjects survive longer than do young mice given the same number of leukemic cells, possibly due to the greater initial weight of the older animals. The older mice appear to tolerate higher doses of aminopterin but the leukemic cells do not.

Dr. Michael Potter has developed murine leukemias which grow in the peritoneal cavities. Some of them exhibit a semi-logarithmic relation between dose of inoculum and duration of survival, thus providing another fine test object for the study of antileukemic drugs. Dr. Potter has also found an experimental reticulum cell sarcoma sensitive to treatment with triethylene melamine and a plasma cell tumor affected by azaserine.

Dr. L. W. Law, collaborating with Dr. A. D. Welch (Yale University), describes analogues of uracil and orotic acid which inhibit bacterial growth and also retard growth of some experimental leukemias. Dr. Law, having developed strains of leukemias sensitive or resistant to the action of various antileukemic drugs, is studying intensively the mechanisms whereby a neoplasm once damaged by a given agent acquires the ability to resist its action completely. Development of drug resistance occurs almost invariably in clinical treatment of leukemias. Dr. Law finds that leukemias to antipurine compounds have a far greater capacity to convert folic acid to citrovorum-factor-like compounds than do leukemic cells that are sensitive to the antipurine drugs. The resistant forms are strikingly sensitive to methotrexate. These results may conceivably indicate a shift in the major pathway of nucleic acid synthesis from one using preformed purines to a system of synthesis employing much

smaller building blocks.

The adenine analogue 4-aminopyrazolo-(3,4,D)-pyrimidine (an antipurine) inhibits partially the growth of all sensitive, resistant and dependent mouse leukemias tested by Dr. S. E. Reaume. The comparable guanine analogue has no such effect but satisfies the anti-purine requirement of a leukemia requiring 8-azaguanine for optimal growth.

Dr. Reaume has also studied the possibility that metabolic cleavage of aminopterin into pteridine and p-aminobenzoylglutamate may play an important role in the acquisition of the resistant state. He has been unable to demonstrate the postulated reaction among any leukemic cells.

Many problems are encountered in determining efficacy of drugs in experimental systems. It is sometimes difficult, for example, to discriminate between lethality due to the disease under study and toxicity of an experimental drug. Dr. Bernard Shacter has provided his colleagues in the Leukemia Studies Section with a useful tool by showing a depression in hepatic glutathione accompanying the growth of an experimental leukemia. Arrest of leukemic growth by drug therapy restores glutathione to higher than normal values.

Fever, a common phenomenon among leukemic patients, has commonly been ascribed to the disease itself. Drs. R. T. Silver, J. P. Utz (NIAID), J. L. Fahey, G. A. Beal (NIAID) and R. W. Kolb (DBS) have made an intensive systematic study of all patients developing fever while hospitalized on the Leukemia Service, NCI. Fever in the great majority of cases is due to complicating and remediable bacterial infection since microorganisms can be isolated and identified during most of the febrile episodes and defervescence follows institution of appropriate therapeutic procedures. The marked susceptibility to bacterial infection does not seem to extend to viral diseases. No difference is observed in the opsonocytophagic indices of mature polymorphonuclear leucocytes in healthy and leukemic subjects. The heightened susceptibility to infection among patients with leukemia apparently relates to the ratio of mature polymorphonuclear leucocytes to the total number of circulating white blood cells rather than to the absolute number of circulating polymorphonuclear forms.

An opportunity to study a patient with leukemia and fluorosis arose during the year. Neither leukemia nor multiple myeloma altered the excretion pattern of fluoride. Patients with and without fluorosis excrete a constant proportion of ingested fluoride, and a patient with fluorosis will continue to excrete fluorides when given only distilled water. A daily intake of 5 mg. of fluoride has no influence on balances of nitrogen potassium, phosphorus, calcium, sodium or chloride, according to Dr. Watkin.

Other Anticancer Drugs

Progress in developing better agents for the treatment of the majority of cancers is impeded for want of an experimental system which predicts clinical experience with a fair degree of accuracy. Substantial research is required before a drug may be introduced into clinical investigation. The aim of the intramural program in chemotherapy of "solid tumors" is to obtain clinical experience as rapidly as possible. Unequivocal evidence of drug effect on the course of human cancer would seem to be obtainable only by using patients whose lesions can be measured. Such individuals may have superficially located cancers, pulmonary metastases which can be delineated on roentgen examination or perhaps patients with osseous metastases in whom alterations in calcium excretion reflect the ebb and flow of their neoplasms, as suggested by Pearson et al. (Memorial Center, New York, N. Y.). The number of cancer patients with suitable lesions is limited even in the larger hospitals, hence Dr. C. G. Zubrod has initiated collaborative research with 5 other institutions to obtain adequate experience in the shortest possible time. The initial venture will determine the relative therapeutic effectiveness of nitrogen mustard and thiotriethylenephosphoramide. Standard procedures have been agreed upon by all participants and frequent meetings of the group provide for rapid exchange of information. Drs. J. H. Tuohy and B. I. Shnider represent the interests of NCI in this venture.

Some anticancer drugs may be expected to produce their effects because of the concentrations they attain in extracellular fluids bathing the cells. Deliberate injection of potentially useful compounds into superficially located metastases, then, might provide information on possible therapeutic effect. Dr. C. O. Brindley is studying this hypothesis systematically. Doses used are minute, and accurate measurements of the metastatic tumors are recorded. The theoretical objection that direct injection of small quantities of innocuous fluids might be expected to alter cancerous growth through increase in intratumoral pressure and other nonspecific effects is not borne out by experience. Dr. Brindley has examined compounds known to affect cancerous growth as well as some of unknown effect. Extensive histological changes may be found on direct injection of antitumor agents before changes in macroscopic appearance or in size, as demonstrated by caliper measurement, can be shown. The quantity of an agent required to cause local regression is relatively large and approaches the systemically administered effective dose in some cases. Additional experience is, of course, required, but the possibility that some of these drugs act through production of some different compound by virtue of metabolic change in the original drug assumes increasing importance.

Correlations between effects of anticancer drugs on local or systemic administration may be obtained from investigations in

laboratory animals. Drs. M. K. O'Gara and Joseph Leiter report such work using alpha peltatin and acetylpodophyllotoxin-omega-pyridinium chloride. Each of these necrotizing agents causes extensive damage in some experimental tumors when given by parenteral injection but a thin rim of viable cancer cells persists about the periphery of the damaged neoplasms. Direct intratumoral injection of the two drugs also causes extensive destruction but viable cells persist about the blood vessels in the cancers. This is paradoxical to some degree. If these agents should act by virtue of the dose delivered directly to the cancer cells, then one would have anticipated a greater effect on those cells adjacent to the blood vessels when administered systemically. The combined experience of local and systemic treatment raises additional questions.

Some analogues of riboflavin retard the growth of experimental tumors. Dr. Montague Lane and colleagues have studied certain riboflavin antimetabolites in cancer patients but have observed no beneficial effects. The question arose as to whether the dichotomy between laboratory and clinical experience might be due to some difference in drug action caused by different metabolic changes in the compound in rat and man or a drug failure per se suggesting some basic difference in neoplasms among the two species. A prototype compound, U-2112, was generously provided by the Upjohn Company, Kalamazoo, Michigan. It produced definite signs of riboflavin deficiency in the rat but not in man. It retarded the growth of two rodent cancers but had no effect on human cancer. Dr. Lane has shown significant differences in the metabolites of U-2112 excreted in the urine by rats and humans which may well account for the differences in therapeutic effect. The drug is poorly absorbed, so the Upjohn workers have developed a comparable compound suitable for parenteral administration, which is now being studied at NCI. The basic question of the effect of riboflavin deficiency on the growth of clinical cancers has not yet been resolved. Dr. Lane's ability to study the fate of the compound has provided essential information. The NCI program will depend heavily on this type of research. Dr. T. L. Loo, for example, is already devising means for measuring 6-mercaptopurine in body fluids.

Filterable Viruses

The approach to filterable viruses as anticancer agents is not new. Substantial progress in defining problems associated with the use of APC viruses in carcinoma of the uterine cervix was reported last year. Drs. R. R. Smith and R. J. Huebner (NIAID) report increased effect on these cancers by the use of cortisone during treatment. Cortisone and virus together produce a transitory febrile episode with general malaise and greater sloughing of the cancer. The evidence currently available does not indicate clearly that cortisone interferes with antibody production, thought to be a serious impediment to effective use of these biological agents. These early results should be exploited.

The investigators have been using comparatively dilute solutions of virus and greater concentrations may enhance their effectiveness. It is also possible that serial treatment with APC viruses of different antigenic structure may be more useful, and, further, that continued residence of APC viruses with human cancers living in experimental systems may permit development of more cancericidal forms. Progress in these types of effort is seriously hampered by inadequate resources, mainly budgetary. An ordinary preparation suitable for clinical use costs about $1 per milliliter to produce, and the measurements made by highly skilled professional and technical personnel are costly but are absolutely essential to provide critically important information. Dr. Huebner is anxious to introduce other viruses into clinical investigation but the means are not at hand to do so now. The limited experience already obtained encourages further and intensified research on the therapeutic use of filterable viruses as agents showing a marked selectivity of action on cancerous tissues.

Dr. E. M. Nadel has observed prolongation of survival among leukemic guinea pigs infected deliberately with the virus of lymphocytic choriomeningitis. The effect was not observed in subjects immunized against the virus. Mr. S. R. Humphreys, Mr. J. M. Venditti and Dr. Abraham Goldin noted a curious alteration in the growth characteristics of a particular murine experimental leukemia which they associated with the presence of an infectious agent. Additional work by Drs. S. E. Stewart and V. H. Haas (NIAID) suggests that infection with lymphocytic choriomeningitis may retard growth of some experimental cancers and may explain in part the observations of their colleagues in the Laboratory of Chemical Pharmacology.

SERVICE FUNCTIONS

A large part of the progress noted in this report has involved collaborative research. Members of the pathology staff have been particularly generous in providing accurate diagnosis and classification of the many lesions that are studied in the NCI. Dr. H. L. Stewart and his associates have prepared a definitive work on experimental tumors that is now ready to be printed and will certainly become a vade mecum of cancer research. The highly developed skills of professional pathologists are equally essential in clinical investigations. The Pathologic Anatomy Branch under the leadership of Drs. H. L. Stewart, L. B. Thomas, A. W. Hilberg and J. H. Edgcomb performed 148 post-mortem examinations and examined 1778 surgical specimens during the year. The case load of exfoliative cytological examinations also continues to increase. Dr. Hilberg has increased usefulness of these techniques by including studies of cell changes in relation to estrogenic activity as a routine function of his staff. The Pathological Technology Section under Mr. J. M. Albrecht

continues to provide excellent histological preparations for all investigators at NCI at minimum cost.

The analytical group in the Laboratory of Biochemistry under the leadership of Mr. R. J. Koegel absorbed a 33 percent increase in work load without using additional personnel.

The NCI is extremely grateful to all of these people and to the Central Services of NIH for the generous support they have provided the research staff.

This report could easily have been much longer, for equally exciting advances not included herein are in prospect. Much remains to be done before the effective control of cancer is achieved. No one, at this time, can predict with reasonable certainty just how the ultimate goal will be attained, but a number of different approaches to our problems are beginning to converge on critically important points. This good sign emphasizes the need for encouraging individual enterprise and initiative.

Respectfully submitted,

G. Burroughs Mider, M. D.
Associate Director in Charge of Research
National Cancer Institute

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PROJECT REPORT FORM

1. National Cancer Institute — INSTITUTE
2. Office of Associate Director in Charge of Research — LABORATORY OR BRANCH
3. Clinical Pathology Department, Clinical Center, N.I.H. — SECTION OR SERVICE
4. — LOCATION (IF OTHER THAN BETHESDA)
5. 201 — SERIAL NO.

6. Ultraviolet Television Microscopy — PROJECT TITLE

7. George Z. Williams, M.D. — PRINCIPAL INVESTIGATOR(S)

8. None — OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

A. OBJECTIVES:

1. Improvement of ultraviolet television microscope instrumentation.

2. Application of ultraviolet television microscopy to study of living cells.

3. Exploration of application of this method to diagnostic cytology
   - marrow
   - cytology of serous fluids, exudates and "exfoliated" cells
   - cytopathology of viral cell cultures.

4. Development of chemical systems for studying metabolic processes in living cells.
   - Tetrazolium - dehydrogenases.

B. METHODS EMPLOYED:

A 2 - 10 mμ band beam, selected in the 255-400 mμ range, is transmitted through a quartz monochromator and reflecting condenser and objective, and the specimen image is focused on the target plate of an ultraviolet sensitive vidicon tube. The closed circuit industrial television system produces the ultraviolet absorption image of the specimen on a kinescope screen suitable for direct observation or photographic record. A special oscilloscope selects any single desired scanning horizontal line traversing the image on the kinescope screen and displays

its characteristics on a cathode ray tube in terms of deflections, representing relative densities of the specimen to the ultraviolet light. Measurements of these deflections are feasible. Errors due to electronic characteristics of the system occur, have been analyzed, and correcting modifications of instrumentation determined. Greatly improved equipment is contemplated and this will make possible more accurate measurements and reproducibility.

Suitability of several recommended ultraviolet light sources have been tested and data on intensity, quenching, etc., accumulated.

A suitable warm stage and 10 and 20μ quartz perfusion chambers were designed and these have been fabricated by the Instrument Section.

For studies in living cell metabolism, the collaborative project with Dr. Pierce, Professor of Chemistry, University of Richmond, has continued. He has synthesized a group of 15 more tetrazolium derivatives for testing. Our evaluation of these compounds includes ultraviolet absorption spectral curves of the tetrazoliums and their formazans, toxicity to mice, and ascites tumor cells in vitro, reduction by ascites tumor cells without added substrate, by mouse liver cells with various substrates and reduction rates.

C. MAJOR FINDINGS:

The ultraviolet television microscope permits rapid scanning and direct observation of large amounts of unstained cytological material, both living and fixed, in a minimum time. Data on various bands of ultraviolet absorption by cellular material is being accumulated more rapidly than has been possible previously.

Although ultraviolet light is very injurious to living cells, this instrument makes feasible brief exposures by quick scanning movement of the specimen through a minute (20 - 40μ^2) illuminated field and shutter interruption of the light during periods of preparation for photography, perfusion, etc.

All of the insoluble formazans absorb strongly between 250 and 380 mμ. They vary in toxicity and reduction rates. Reduction of several within the living cell has been observed within minutes at extremely low concentrations and can be visualized at the location of mitochondria.

Remarkable variations in ultraviolet absorption maxima of nuclei of normal and mouse ascites tumor cells are consistently observed.

Considerable diagnostic assistance has been accomplished, by examination of fresh smears of bone marrow in cases of suspected leukemia and bizarre anemia. Hematoporphorin and precursors in the cytoplasm of early erythroblasts intensely absorb ultraviolet at 410 mμ and thus differentiate these blast forms in diagnosis.

D. SIGNIFICANCE TO NCI:

Exploration of the application of ultraviolet television microscopy to cell studies indicates that localization and direct observation of metabolic products or ion toxic indicators which absorb ultraviolet is feasible in living cells. Such studies will contribute to knowledge of processes in living cell systems and the differences which may exist between normal and abnormal (including cancer) and changes produced by injury, and therapeutic agents.

More rapid and reliable laboratory diagnosis of marrow lesions is possible with aid of this method.

E. PROPOSED COURSE OF PROJECT 201:

1. Further improvement of instrumentation.

2. Improvement of technics for preparing and maintaining living cells for study of metabolic changes by perfusion.

3. Exploration of various biochemical systems for indicating metabolic products by ultraviolet absorption.

4. Changes in living cells subjected to ultraviolet and X-ray irradiation.

5. Comparison of ultraviolet absorption patterns in living and variously fixed cells.

6. Study of possible early cytopathologic changes in tissue culture cells caused by viruses.

7. Continued accumulation of ultraviolet absorption data on fresh preparations of marrow and cytology specimens from patients.

10. 201
SERIAL NO.

11. NCI
BUDGET ACTIVITY

RESEARCH [X] ADMINISTRATION [ ]

REVIEW & APPROVAL [ ] TECHNICAL ASSISTANCE [ ]

12. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 or 1957

Oncology Department, Medical College of Virginia, and
Department of Chemistry, University of Richmond
Dr. Stanley Pierce, Professor of Chemistry - Preparation of tetrazolium derivatives.

13. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

None

4. 201
SERIAL NO.

5. PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1955

Convention Record, IRE, Vol. 3, Pt. 9, pg. 131, 1955

NOTE: Three demonstrations and accompanying reports on the Instrumentation and Application of Ultraviolet Television Microscopy in Medical Research were presented at:

N.Y.C. - IRE Annual Convention, Medical Electronics Symposium, March 1955
Denver, Colorado - Rocky Mountain Radiological Conference, August 1955
Washington, D. C. - Symposium on Electrical Technics in Medicine, November 1955

16. HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1955.

None.

PROJECT REPORT FORM

1. Cancer INSTITUTE | 2. Office Assoc. Director in Chg. Research LABORATORY OR BRANCH

3. Environmental Cancer Section SECTION OR SERVICE | 4. LOCATION (IF OTHER THAN BETHESDA) | 5. DADB-202 SERIAL NO.

6. Carcinogenic Studies on Aromatic Amines and Food Dyes
PROJECT TITLE a) Experimental Aspects
b) Epidemiologic Aspects

7. W. C. Hueper
PRINCIPAL INVESTIGATOR(S)

8. J. Cole (Surgical Procedures)
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objective: The widespread contact of the human population for occupational, dietary or other environmental reasons with aromatic amines used as antioxidants in rubber, as parts of dyes, in foods, medicines, cosmetics, household goods, industrial products and paints, or as "whitening" phosphors in household detergents, and the demonstration of cancerous reactions in humans having contact with a few of these products and in animals exposed to many others, provided the incentive for ascertaining the potential scope of human cancer hazards from such sources.

Methods Employed: The methods used were of both experimental and epidemiologic nature, and applied to humans as well as experimental animals.

a) In one of several experimental approaches adopted, isolated pouches from various parts of the gastrointestinal tract of dogs were prepared and paraffin pellets containing between 2 to 3 gms. of one of several aromatic amines (beta-naphthylamine; 4-aminodiphenyl; benzidine; yellow AB) were embedded in the lumina of these pouches, which were left with their normal blood supply intact either within the abdominal cavity or within the subcutaneous tissue of the anterior abdominal wall. The dogs will be observed for several years for the possible development of cancers from the mucosa of these pouches.

b) In a second series of experiments the ureters were implanted into the colon and paraffin pellets containing the same aromatic amino compounds were left in the bladder which was ligated at its urethral orifice to prevent the escape of the pellet.

PROJECT REPORT FORM(cont'd).

10. OADR-202
SERIAL NO.

9. PROJECT DESCRIPTION (cont)

Methods employed: (cont) The dogs which die are subjected to histologic study of the bladder and internal organs for evidence of neoplastic reactions. Because of the more intense contact of the bladder mucos with the cancerigenic chemicals, there is the possibility that such development may occur within a shorter latent period than that observed after oral feeding.

c) A third experimental approach in which yellow AB, a certified food dye, is studied in man and experimental animals for the chemical nature of metabolites formed, was assigned to Dr. Malloy and is reported by him.

d) Preparations are being made with the approval and cooperation of Arm and Navy Officials, to conduct an epidemiologic survey of workers employed in several arsenals of the Army and Navy for determining whether workers employed in the manufacture of colored smoke ammunition and handling dyes which in part have produced cancers in experimental animals, exhibit any abnormalities in their cancer incidence, especially as the incidence of cancer of the bladder, liver and intestine.

Major Findings: None.

Significance to Cancer Research: The experimental investigations might provide important information concerning a possible carcinogen action of aromatic amines on the gastrointestinal mucosa, which in turn would suggest that exposures of such nature sustained by humans for occupational or dietary reasons might account for some of the gastrointestinal cancers observed The epidemiologic data would supply information concerning the applicability o observations made in relation to the carcinogenicity of dyes in experimental animals to the human population similarly exposed.

Proposed Course of the Project: The dogs in the experiment will be observ and when dead studied by histopathologic procedures.

The epidemiologic surveys on workers employed during the past 20 years in Army and Navy arsenals will be undertaken if present exploratory steps demonstrate the practicability of this study.

11. RESEARCH
BUDGET ACTIVITY

NO ENTRIES FOR ITEMS 12, 13, 14 & 16.

15. Hueper, W. C., Environment and Cancer. J. A. M. A. 157:679, 1955.
PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 55

PROJECT REPORT FORM

Cacer INTITUTE | 2. Office Assoc. Dir. in Chg. of Research LABORATORY OR BRANCH

Erironmental Cancer Section SETION OR SERVICE | 4. LOCATION(IF OTHER THAN BETHESDA) | 5. OADR-203 SERIAL NO.

Macromolecular Polymers as Carcinogenic Agents
PROJECT TITLE

W. C. Hueper
PINCIPAL INVESTIGATOR(S)

OTHER INVESTIGATORS

ROJECT DESCRIPTION

bjectives: The experimental production of cancers in rats and mice by the parenteral implantation of water insoluble polymers used as plastics, films, resins and rubbers, raised the question whether imilar properties are possessed by water soluble synthetic polymers, articularly those used as plasma substitutes or as mucilagenous thickeners of nd additives to foodstuffs and medicines, and whether such properties are ependent on molecular size and shape.

ethods Employed: Seven different types of polyvinyl pyrrolidone of American and German manufacture and varying in average molecular size between 10,000 and 300,000 and nine different kinds of dextran of a molecular size range between 20,000 to 500,000 and of straight and branched olecular shape are tested. For comparative purposes the following macromolecular polymers are studied or will be studied:- polyvinyl alcohol, methyl cellulose, ethyl cellulose, soluble starch and diethyl silicone as well as silicon dioxide. The material was implanted in powdered form into the subcutaneous tissue and the peritoneal cavity of mice and rats and was intravenously injected in a saline solution into rats and rabbits. Rats and rabbitS are subjected to periodic studies of blood reactions to the macromolecular material.

Major Findings: About 30 per cent of the rats receiving PVP developed within 18 months after the administration of this chemical by subcutaneous, intraperitoneal or intravenous route, cancers originating from reticuloendothelial cells of lymph nodes, from Kupffer cells of the liver or from uterine structures. The first cancerous reactions appeared after 6 months. None so far have been observed in mice or rabbits. None were seen in mice, rats and rabbits given dextran, which had been exposed for more than one year. Rats repeatedly stored with PVP showed marked hematic mononucleoses, while rabbits intravenously injected with dextran developed a basophilic and a clotting defect.

PROJECT REPORT FORM (Cont)

10. OADR-203

9. PROJECT DESCRIPTION(Cont):

Significance to Cancer Research: 1) The observations made indicate th not only apparently water insoluble or little soluble carbon and silicon polymers are capable of eliciting cancers in exp mental animals at the sites of deposition, but that also highly water soluble polymers, medicinally used, must be suspected of having such pr ties.

2) Because of the retention of PVP i organs containing phagocytic reticuloendothelial cells, such as the lymph nodes and the liver, cancers originated not at sites of primary contact but in organs of deposition.

3) Since PVP has extensively been employed as a plasma substitute and is widely used as an act vehicle in other medicinal preparations as well as in certai cosmetic products, the observations made are of distinct importance fro public health viewpoint.

The results so far obtained have therefore been made available to the National Research Counc and to health authorities in Canada and England, as well as American industries manufacturing or merchandising PVP preparations.

Proposed Course of Project: The present experiments will be continued. Rats and rabbits are being subjected to repeated and periodi subcutaneous and intravenous administrations of large amount of PVP and dextran in an attempt to increase the cancer attack rate in rats and to properly determine whether rabbits after comparable exposur to these agents, may also develop cancers.

A report on the first phase of these exper ments is being prepared for publication.

11. Research
BUDGET ACTIVITY

NO ENTRIES FOR ITEMS 12, 13, 14 and 15.

16. October 7, 1955 - INVITED ADDRESS:-"Cancers Produced with Macromolecule (HONORS AND AWARDS) Annual Meeting, Coordinators of Cancer Teaching.

PROJECT REPORT FORM (Cont)

10 OADR-203

9. PROJECT DESCRIPTION(Cont):

Significance to Cancer Research: 1) The observations made indicate that not only apparently water insoluble or little soluble carbon and silicon polymers are capable of eliciting cancers in experimental animals at the sites of deposition, but that also highly water soluble polymers, medicinally used, must be suspected of having such properties.

2) Because of the retention of PVP in organs containing phagocytic reticuloendothelial cells, such as the lymph nodes and the liver, cancers originated not at sites of primary contact but in organs of deposition.

3) Since PVP has extensively been employed as a plasma substitute and is widely used as an active vehicle in other medicinal preparations as well as in certain cosmetic products, the observations made are of distinct importance from a public health viewpoint.

The results so far obtained have therefore been made available to the National Research Council and to health authorities in Canada and England, as well as to American industries manufacturing or merchandising PVP preparations.

Proposed Course of Project: The present experiments will be continued. Rats and rabbits are being subjected to repeated and periodic subcutaneous and intravenous administrations of large amounts of PVP and dextran in an attempt to increase the cancer attack rate in rats and to properly determine whether rabbits after comparable exposure to these agents, may also develop cancers.

A report on the first phase of these experiments is being prepared for publication.

11. Research
BUDGET ACTIVITY

NO ENTRIES FOR ITEMS 12, 13, 14 and 15.

16. October 7, 1955 - INVITED ADDRESS:-"Cancers Produced with Macromolecules": (HONORS AND AWARDS) Annual Meeting, Coordinators of Cancer Teaching.

PROJECT REPORT FORM

ancer | 2. Office Assoc. Dir. in Chg. Research
INSTITUTE | LABORATORY OR BRANCH

nvironmental Cancer Section | 4. | 5. OADR-204
SECTION OR SERVICE | LOCATION (IF OTHER THAN BETHESDA) | SERIAL NO.

arcinogenic Studies on Petroleum Substitutes and Synthetic Liquid Fuels.
PROJECT TITLE II. Bergius Oils and Fischer-Tropsch Oils
III. Carcinogenicity of Shale Oil Fractions of Low Boiling Point and Free of 3,4-Benzpyrene

', C. Hueper
PRINCIPAL INVESTIGATOR(S)

OTHER INVESTIGATORS

ROJECT DESCRIPTION

bjectives: The present project is a continuation and elaboration of studies started several years ago for determining the carcinogenicity of crude and processed hydrocarbon products obtained by the retorting of oil shale and the direct or indirect hydrogenation of coal, recently introduced into American industries.

a) Shale Oil

lethods Employed: Fractions of shale oil having a boiling point below 700° F. and found by Dr. H. Cahnmann to be spectrophotometrically free from 3,4-benzpyrene, were injected into the thigh muscle of C57 black mice. The fractions used covered a range between heavy oils to products representing crude gasoline.

Major Findings: Cancerous reactions were elicited in some of the mice with practically all fractions. These lesions were most frequently obtained with the low boiling fraction.

Significance to Cancer Research: The observations made establish the carcinogenic potency of crude and processed American shale oils and demonstrate that not only products having a boiling point above 700° C. possess carcinogenic properties, but that such qualities are also present in oils of a much lower boiling point. These findings are in agreement with recently reported observations concerning the carcinogenic potency of certain low boiling products obtained by the fractionation of coal tar and petroleum oils.

Proposed Course: The bioassay studies will be terminated during the next year and the project will come to an end since its primary objective has been obtained.

PROJECT REPORT FORM (CONT)

10. OADR-204
SERIAL NO.

9. PROJECT DESCRIPTION (cont)

b) Bergius and Fischer-Tropsch Oils

Methods Employed: Nine fractions obtained from coal by the Bergius process and five fractions obtained by the Fischer-Tropsch process covering the entire boiling range of products resulting from t two manufacturing methods of petroleum substitutes (from coke to purified gasoline) were tested on mice, rats and rabbits, by repeated application to the skin of mice and rabbits and by intramuscular injection into rats.

Major Findings: Cancerous reactions were produced in mice, rats and rabbit with most of the fractions tested. Only purified gasoline was consistently negative.

Significance to Cancer Research: The observations made extend the range of occupationally and environmentally important products possessi carcinogenic properties to substances only recently introduced to the American scene. Their scientific and practical importance is attest to by the fact that two cases of skin cancer in workers engaged in the manufacture of these products were observed within the last two years.

Proposed Course of Project: The present experiments are almost concluded. A final evaluation of the results obtained will be made. Sinc plants of the U. S. Bureau of Mines providing the products use were closed, the investigation will be discontinued. Final reports are being prepared.

11. Research
BUDGET ACTIVITY

NO ENTRIES FOR ITEMS 12, 13, 14, 15 and 16.

PROJECT REPORT FORM

Cacer INTITUTE	2. Office Assoc. Dir. in Chg. Research LABORATORY OR BRANCH	
Environmental Cancer Section SETION OR SERVICE	4. LOCATION(IF OTHER THAN BETHESDA)	5.OADR-205 SERIAL NO.

Experimental Studies in Metal Cancerigenesis
PROJECT TITLE

W. C. Hueper
PRINCIPAL INVESTIGATOR(S)

W. W. Payne
OTHER INVESTIGATORS

PROJECT DESCRIPTION

Objectives: Epidemiologic evidence from American and/or foreign industries incriminates exposure to certain metals or metal compounds (chromium, nickel, arsenic, beryllium, asbestos, uranium) in the production of cancers of the respiratory tract (lung, nasal cavity, nasal sinus) among the workers. Since some of the most important and fundamental aspects of metal carcinogenesis affecting possibly large and diverse worker groups cannot be properly studied in humans, a comprehensive experimental program of metal carcinogenesis was started several years ago.

Methods Employed: Finely powdered metals were suspended in a viscous vehicle (lanolin, gelatin solution) and were implanted into the marrow cavity of the femur, the pleural cavity, the peritoneal cavity, muscle tissue and nasal sinus of mice, rats, guinea pigs, rabbits and dogs or injected intravenously into mice, rats and rabbits. Rats, guinea pigs and rabbits were placed into chambers where they were exposed to dust of powdered nickel and chromite ore. These steps were taken for eliciting cancers. Rabbits were intravenously injected with chromium-protein complexes for the production of metal specific antibodies to be used, if successful, in the development of biology specific diagnostic tests, indicating previous biologically effective exposure to a particular carcinogenic metal.

Major Findings: Chromium or chromite ore parenterally introduced, produced only a few cancers in rats at the sites of deposition(fibrosarcoma) or remote from them (pancreatic insuloma, pulmonary papilloma and carcinoma), for which a causal relation to the metal might be suspected. No tumors developed in any other species.

Nickel implants made in the subcutaneous tissue and marrow cavity of the femur of rats elicited sarcomas at the site of deposition in about 28% of the rats thus exposed. One out of six rabbits with an intrafemoral implant developed an endosteal sarcoma. Tumors were not obtained in mice or dogs.

PROJECT REPORT FORM (cont)

10. OADR-205
SERIAL NO.

9. PROJECT DESCRIPTION(cont)

Significance to Cancer Research: The carcinogenicity of chromium may be species specific and limited to the human species or species not included in the present investigation. Chromium may thus resemble in its carcinogenic peculiarities those apparently possessed by arsenic. On the other hand, chromium by itself may not be carcinogenic but may require some specific but unknown activator to become effective, or the cancer hazard of chromate manufacturers may causally be related to chemicals other than chromium compounds.

The carcinogenicity of metallic nickel for two species (rats and rabbits) can be considered as established. The causation of carcinomas in the nasal cavity, nasal sinuses and lungs of nickel refinery workers by a specific action of nickel fumes or vapors inhaled is thereby made most likely if not established.

Proposed Course of Project: Observation of rats intramuscularly and intrapleurally injected with chromite ore roast suspended in lamb's fat will be continued.

The long term inhalation experiment on rats and guinea pigs which are being exposed to chromite ore dust will likewise be maintained.

A reactivation of chemoimmunity experiments conducted during 1954 is contemplated if proper personnel arrangements can be made. Preparations for the future study of artificially produced chromium-nucleoprotein complexes are made.

Inhalation experiments in which rats and guinea pigs are exposed to nickel dust will be continued.

11. RESEARCH
BUDGET ACTIVITY

NO ENTRIES FOR ITEMS 12, 13 and 14.

15. PUBLICATIONS:- Hueper, W. C., Experimental Studies in Metal Cancerigenesis IV. Cancer Produced by Parenterally Introduced Metallic Nickel. J. Nat. Cancer Inst. 16:55-73, 1955.

Hueper, W. C., Experimental Studies in Metal Cancerigenesis VII. Tissue Reactions to Parenterally Introduced Powdered Metallic Chromium and Chromite Ore. J. Nat. Cancer Inst. 16:447-469, 1955.

Hueper, W. C., Silicosis, Asbestosis and Cancer of the Lung. Am. J. Clin. Path. 25:1388-1390, 1955.

16. Sept. 12 & 13, 1955-Conference of the Study Section on Environmental Carcinogens, NCI. Stone House, NIH. "Nickel Carcinogenesis", by invitation of

PROJECT REPORT FORM

1. Cancer INSTITUTE
2. Office of the Assoc. Dir. in Chg. Research LABORATORY OR BRANCH
3. Environmental Cancer Section SECTION OR SERVICE
4. LOCATION(IF OTHER THAN BETHESDA)
5. OADR-206(a) SERIAL NO.

6. Studies in Carcinogenic Water Pollutants. II. Carbon Adsorbates from Effluents of a Coke Plant. PROJECT TITLE

7. W. C. Hueper PINCIPAL INVESTIGATOR(S)

8. OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: The demonstration of marked regional variations in the relative frequency of cancers of the alimentary tract suggests that local differences in the character and/or amounts of environmental, particularly, dietary agents possessing carcinogenic properties, might account to some degree for these fluctuations. Since carcinogenic pollutants of water employed for human consumption as drinking water or used by vegetable and animal life furnishing foodstuffs might supply such exposures, studies were undertaken for demonstrating the presence of carcinogenic factors originating from industrial sources in raw water. Previous investigations had shown such agents in raw water contaminated by effluents of an oil refinery. The present experiments extend these studies to carbon adsorbates prepared from raw water polluted with effluents of a coke oven plant. The project on oysters obtained from waters polluted with ship fuel oil assigned to and reported by Dr. H. Cahnmann, represents an additional extension of this project.

Methods Employed: C57 black mice are painted twice a week with the eluate.

Major Findings: None

Significance to Cancer Research: The prolonged and often life-long exposure of humans to carcinogenic matter contained in foodstuffs might well provide the cause for the development of cancers in the alimentary tract. Studies of the described type therefore, might provide clues concerning the sources and types of specific exposures sustained by different populations and their relation to epidemiologic differences in the incidence of gastrointestinal cancers.

Proposed Course of Project: Continued application of the Adsorbate to mice.

10. RESEARCH

12. Adsorbate was supplied by Sanitary Engineering Center, U.S. Public Health Service, which studies the chemical aspects of these adsorbates in this cooperative venture.

ENTRIES FOR ITEMS 13, 14, 15 and 16.

12/22/55

PROJECT REPORT FORM

1. Cancer
INSTITUTE

2. Office Assoc. Director in Chg. Research
LABORATORY OR BRANCH

3. Environmental Cancer Section
SECTION OR SERVICE

4. 5 OADR-206 (b)5
LOCATION (IF OTHER THAN BETHESDA) SERIAL NO.

6. Polynuclear aromatic hydrocarbons in oysters --Project B
PROJECT TITLE

7. H. J. Cahnmann
PRINCIPAL INVESTIGATOR(S)

8. M. Kuratsune
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: The objective of this investigation is to determine whether appreciable amounts of polynuclear aromatic hydrocarbons, particularly those in the "carcinogenic range" (i.e., those containing 4 - 6 condensed rings) are present in oysters collected in polluted water.

Methods Employed: Oysters collected in badly polluted water were exhaustively extracted with methanol after removal of the shells. The methanolic extract was further fractionated by solvent partition and saponification. The non-saponifiable fraction thus obtained was subjected to multiple chromatographic fractionations, using a number of different adsorbents and development methods (cf. project A). These fractionations are still being continued. Between 100 and 200 fractions have been obtained so far. They all have been evaluated spectrophotometrically. Samples of individual polynuclear aromatic hydrocarbons and of related aza compounds (most of them only available in an impure state) are being purified chromatographically. Then their absorption spectra (and in some cases their fluorescence spectra) are being determined. These spectra serve to identify the spectra of oyster extract fractions.

Major findings: The non-saponifiable fraction obtained from 5 kg of shell-free oysters contains a small amount of polynuclear aromatic hydrocarbons, apparently considerably less than the amount found by Zechmeister and Koe in certain batches of barnacles. The "hydrocarbon fraction" amounts to roughly 500 mg; however, a considerable percentage of this amount appears to represent hydrocarbons other than polynuclear aromatic ones. So far, the presence of naphthalenes (2 rings), pyrene, fluoranthene and chrysene (4 rings) has been proven, the presence of benz(a)anthracene (4 rings) or a derivative thereof made almost certain, and the presence of phenanthrenes (3 rings) suspected. Trace amounts of either benzo(a)pyrene (5 rings) or a structurally closely related substance have been detected. This compound is being investigated further. The hydrocarbon fraction of the non-saponifiable material contains weakly fluorescent substances not belonging to the group of the polynuclear fully aromatic hydrocarbons. They

PROJECT REPORT FORM (cont)

10. OADR-206 (b)
SERIAL NO.

9. PROJECT DESCRIPTION(cont) Project B(cont)

Major findings(cont):

are supposed to be at least partly aliphatic or naphthenic. A sterol has also been isolated from the non-saponifiable fraction in pure form. It is probably ostreasterol, a rare sterol described by W. Bergmann. A number of yellow and green pigments are also present in the non-saponifiable fraction, and furthermore a material that forms a colloidal solution with water and a transparent gel with cyclohexane, or n-pentane. This material which is perhaps derived from a phosphatid forms a brium salt not yet investigated.

Significance to cancer research: It has been shown by Zechmeister et al. that certain marine animals, such as barnacles, are able to take up polynuclear aromatic hydrocarbons from their surroundings and to store them in their body. From a public health point of view it is of greater interest to show whether such edible marine animals as e.g. oysters, behave similarly.

Proposed course of project: The identification of the individual polynuclear hydrocarbons in the investigated batch of oysters is to be continued. Some of the other constituents of the non-saponifiable fraction should be better characterized. It will be of interest to investigate whether polynuclear aromatic hydrocarbons can also be found in oysters collected in less polluted or in practically non-polluted water.

11. Research
BUDGET ACTIVITY

NO ENTRIES FOR ITEMS 12, 13, 14, 15 and 16.

12/22/55

PROJECT REPORT FORM

1. Cancer 2. Office of the Assoc. Director in Chg. Res.

3. Environmental Cancer Section 4. _____ LOCATION(IF OTHER THAN BETHESDA) 5. OADR-207 SERIAL NO.

6. Carcinogens in American Shale Oil - PROJECT D -

7. H. J. Cahnmann

8. None

9. PROJECT DESCRIPTION:

Objectives: After the presence of benzo(a)pyrene in American shale oil had been established and the amount of benzo(a)pyrene present evaluated quantitatively, it was of interest to determine whether carcinogens other than benzo(a)pyrene are present in shale oil.

Methods employed: A large number of chromatographic fractions and of distillate fractions which were obtained previously during the fractionation of shale oil and which were shown to be free or essentially free from benzo(a)pyrene, were worked up in order to make them suitable for bioassays. This included removal of solvents, removal of paraffin where necessary and incorporation into a suitable solvent. The resulting samples were submitted to Dr. Hueper for bioassays.

Major findings:)
)
Significance) See Dr. Hueper's report
)
Proposed Course of Project)

11 Research

NO ENTRIES FOR ITEMS 12, 13, 14 and 16.

15. PUBLICATIONS: Detection and Quantitative Determination of Benzo(a)pyrene in American Shale Oil, Anal. Chem. 27,1235(1955) - This publication deals with the methods used in the fractionation of shale oil and not with the results obtained in the bioassays.

PROJECT REPORT FORM 12/22/55

Cncer
ISTITUTE

2. Office Assoc. Dir. in Chg. of Research
LABORATORY OR BRANCH

Ivironmental Cancer Section
SECTION OR SERVICE

4.

5. OADR-208
LOCATION(IF OTHER THAN BETHESDA) SERIAL NO.

Iperimental Studies in Metal Cancerigenesis, Chromium
ROJECT TITLE

Oarles H. Grogan
RINCIPAL INVESTIGATOR(S)

THER INVESTIGATORS

ROJECT DESCRIPTION

roject: - Metabolism of Chromium and Certain of Its Compounds

ubproject A:

bjectives: In view of the high incidence of cancer of the lung in primary chromium producing and processing industry, it is desired to attempt to ascertain the etiologic factor or factors involved.

ethods Employed: Chromite ore, which is the source of chromium in all primary chromium producing and processing industry, although hemically resistant to most dissolving agents (acids) is dissolved by xidative alkaline fusion. It is commonly observed in autopsy specimens of the ung as a brownish deposit. Since the particle size for maximum alveolar etention is in the neighborhood of 1 micron (depending on density) and the imiting size for passage of the nasal filter is around 5 microns, it was elieved that such small particles of chromite ore (0-4 microns particle size) ight be oxidatively dissolved in the lung in the presence of the salts present n the body fluids and the pH's above 7 encountered there.

Powdered chromite ore was fractionated into particles in the range 0-4 and 4-8 microns. Powdered metallic chromium (for which here is little reported evidence of carcinogenicity) was prepared likewise for purposes of comparison. In vitro aeration experiments were carried out in various arrangements of aeration tubes and buffer ionic strength and pH (between 6 and 8) employing the chromite ore fractions and metallic chromium fractions. The microgram and submicrogram amounts of chromium dissolved were detected by analytical methods adapted from those previously reported in this study.

During the progress of the work with chromite ore information reached the section relative to the increased incidence of cancer of the lung among iron (hematite) mining workers. In some of the later experiments, simultaneous solubilization of iron along with chromium from the chromite was studied.

PROJECT REPORT FORM(cont)

10. OADR*208
SERIAL NO.

9. PROJECT DESCRIPTION

Major Findings: The solubilization-aeration experiments with micron and submicron size particles of metallic chromium and chromite ore in various buffer media at pH's between 6 & 8 indicate that all amounts of chromium reported in the blood, urine and tissues of workers in primary chromium producing and processing plants can be accounted for by the oxidative solubilization of chromite ore inhaled and deposited in the lung of the worker. That the process involved in vitro is necessarily an oxidative solubilization was proven by aeration of chromite ore under identical conditions with a stream of nitrogen carefully freed of oxygen by passage through a series of absorption towers of vanadous sulfate and suitable scrubbing and washing towers following the oxygen removing solutions. No increase in chromium content in the aeration media (above the initial blank value) in the nitrogen experiments was observed in a period of 6 weeks.

The rate and extent of solubilization is a function of particle size since (as would be expected for the greater surface area for the same mass) the chromium concentration reached a smaller value in the same time with the 4-8 micron fraction than with the 0-4 micron fraction, which fraction is also of greatest biological interest. Solubilization of metallic chromium by the same processes was significantly slower than that of chromite ore.

The particle size distribution of the fractions collected has been evaluated from electronphotomicrographs and the mass mean density is being evaluated.

Significance to Cancer Research: In this particular field of industrial cancer from environmental causes, the highly excessive incidence of cancer of the lung in primary chromium producing and processing industry (some 29-30 times normal incidence) has been somewhat mystifying as to the causal agent and inability (at least until the present) to reproduce similar lesions in laboratory animals with several of the materials encountered in this industry. The thesis is advanced as a result of these yet incomplete studies that inhaled chromite ore dust (and to a lesser extent metallic chromium) acts as a reservoir of deposited chromium feeding microgram and submicrogram quantities into the body and in particular the lung tissues surrounding the deposits. The materials have previously been considered physiologically inert, although Hueper and Mancuso suggested that chromite ore might be a factor in pulmonary cancer in the chromium industry.

Proposed Course of the Project: The in vitro chemical studies will probably be completed within the next two months. It is proposed to deposit the smaller size fraction (0-4 microns) of chromite ore (and perhaps metallic chromium) into the lungs of animals, rabbits, by an operative technique that will preclude entry by ingestion and then to ascertain chromium levels in the various remote and barrier-isolated tissues, i.e., brain, testes, as a test of the reservoir hypothesis. Other in vivo experiments may be devised depending on the outcome of initial experiments.

PROJECT REPORT FORM(cont)

10. OADR-208
SERIAL NO.

9. PROJECT DESCRIPTION

Project: - Metabolism of Chromium and Certain of Its Compounds

Subproject B: Interaction of chromium compounds with proteins:

Methods: Previous work employing egg proteins and human plasma indicated binding of both Cr^{III} and Cr^{VI} to these proteins. These studies were conducted in conjunction with immunological studies in progress with Cr^{III} and Cr^{VI} protein complexes. Equilibrium dialysis and modified equilibrium dialysis techniques were employed to ascertain binding to proteins.

Major Findings: In addition to those findings reported previously, studies have continued with purified individual human plasma protein components. At physiological pH (7.35) of blood both Cr^{III} and Cr^{VI} are bound to human serum albumin. Cr^{VI} is not bound by human gamma globulin under the same conditions.

Significance to Cancer Research: The protein-chromium binding studies are part of the overall program directed toward the discovery of the etiologic factor in lung cancer of workers in primary chromium producing and processing plants. It is possible that chromium or one of its chemical compounds is this factor.

Proposed Course of Project: It is projected that the investigation of chromium III and VI compounds and their combination with proteins be extended from plasma proteins to lung tissue proteins and nucleoproteins. The interaction studies are primarily conducted in connection with immunological investigation of certain chromium haptens in the hope of developing a practical test that could detect exposure of workers to chromium or its compounds.

Note: During the course of the dialysis studies of chromium-protein combinations certain dialysis techniques were adapted in collaboration with Dr. Elizabeth Roboz of Georgetown University Medical School for the concentration of biological fluids of low protein content. This has proven to be a very useful technique to workers in biochemistry and physiology desiring to assay or isolate proteins from such fluids as urine, cerebrospinal fluid, ascitic and cyst fluids, as evidenced by over 450 requests for reprints of this article.

11. Research

NO ENTRIES FOR ITEMS 12, 13, 14, 15 and 16.

PROJECT REPORT FORM

1. Cancer INSTITUTE
2. Office of Assoc. Director in Chg. Research LABORATORY OR BRANCH
3. Environmental Cancer Section SECTION OR SERVICE
4. LOCATION(IF OTHER THAN BETHESDA)
5. OADR-209 SERIAL NO.
6. Medicolegal and Public Health Activities and Considerations on Occupational, Environmental and Traumatic Cancers
7. W. C. Hueper PRINCIPAL INVESTIGATOR(S)
8. OTHER INVESTIGATORS
9. PROJECT DESCRIPTION

Objectives: The rapid increase in factual knowledge on the actual and potential exogenous causes of human cancers has brought about an augmented awareness of environmental cancer hazards and has necessitated continuous adjustments and modifications in previously existing concepts and attitudes toward these conditions for medicolegal reasons and in considerations of their importance as public health hazards. The numerous data, observations and interpretations of information on environmental cancers continuously collected and evaluated were used for the clarifications of often complex situations and for integrating, systematizing and coding the available evidence for the purpose of its competent and rational use in medicolegal and public health respects.

Methods Employed: All published data related to environmental cancer hazards and carcinogens were collected and assessed as to their scientific and practical significance to the human problems.

Expert opinions were rendered to the Bureau of Employees' Compensation, U. S. Department of Labor, in a considerable number of claims for compensation advanced because of an allegedly occupational or service-connected traumatic origin of cancers which developed in employees.

A monograph on the scope and methods of control of potential cancer hazards from food additives and contaminants was prepared for the Food Protection Board, National Research Council, on its request.

Major Findings: 1. The evidence on hand indicates that environmental carcinogenic agents may account for a considerable number, if not the majority of human cancers affecting various organs and tissues.

2. The existing knowledge on environmental carcinogenesis is highly defective and suffers from lack of medical awareness of and interest in the problem, from an almost complete absence of

PROJECT REPORT FORM(cont)

10. OADR-209
SERIAL NO.

9. PROJECT DESCRIPTION(cont)

Major Findings(cont):

reporting of cases of occupational cancer by the parties concerned, and from insufficient funds, facilities and personnel for an adequate study.

Significance to Cancer Research: Cancer control by preventive measures cannot be practiced without factual knowledge on the causes of cancers and the conditions of exposure to the causal agents. Environmental agents are at present the only established causes of human cancer. Any additions to this knowledge and any improvements in the interpretation of the existing data and their practical application are therefore, of direct and considerable significance to cancer research applied to the human problem.

Proposed Course of Project: Efforts to acquire and collect data on environmental human carcinogenesis will be continued. Such data will be evaluated for their scientific and practical value. This information will be disseminated in publications, addresses, and expert opinions. Preparations are being made for the organization and agenda of a Symposium on potential cancer hazards from food additives and contaminants to be held at Rome, Italy, in August 1956 and sponsored by the International Union Against Cancer.

11.
BUDGET ACTIVITY

NO ENTRIES FOR ITEMS 12, 13 and 14.

15. PUBLICATIONS:

Hueper, W. C., Occupational Cancer Hazards. Safety Standards, Bureau Labor Standards, 4:1-4, 1955.

Hueper, W. C., Occupational Cancer Hazards, Proc. 40th Ann. Conv. Internat. Assoc. Industr. Acc. Boards & Commissions, 1954, Bull. 180, U. S. Depart. Labor, 1955, p. 126-144.

Hueper, W. C., Medicolegal Aspects of Cancer. Am. J. Clin. Pathol. 25:116-125, 1955.

Hueper, W. C., Considerations for the Selection of Chemicals for Carcinogen Screening. Arch. Industr. Health. 11:494-504, 1955.

Hueper, W. C., Environmental and Occupational Cancer Problems in Ohio. Ohio Health. 7:6-13, 1955.

Kotin, P. and Hueper, W. C., Relationships of Industrial Carcinogens to Cancer in the General Population. Publ. Health Rep. 70:331-333,195

PROJECT REPORT FORM(cont)

10. OADR-209
SERIAL NO.

15. PUBLICATIONS(cont)

Hueper, W. C., Trauma and Cancer, J. A. M. A. IN Press.

Hueper, W. C., Causal and Preventive Aspects of Environmental Cancer. Minnesota State Med. J., in press.

Hueper, W. C., Prevention of Cancer, in 2nd edition of Treatment of Cancer and Allied Diseases, Editors, Pack and Ariel. Publishers:Hoeber-Harper, New York.

Hueper, W. C., Environmental Cancer, in 2nd Edition, Physiopathology of Cancer, Editors, Homburger and Fishman, Publishers: Hoeber-Harper, New York.

Hueper, W. C., Environmental Factors in the Production of Human Cancer, in CANCER, Editors:- Lord Horder and R. W. Raven, Publishers: Butterworth's, London, England.

16. ADDRESSES BEFORE SCIENTIFIC SOCIETIES GIVEN BY INVITATION:

Jan. 24, 1955 - Scientific Session of Council on Industrial Health, A. M. A. Clinical Center Auditorium. Address:- "Occupational Cancer - An Industrial Disease Problem." Chairman: Dr. J. M. Lynch, NIH.

February 2, 1955 - Seminar - Institute for Cancer Research, The Lankenau Hospital, Philadelphia. "The Significance of Epidemiologic and Experimental Evidence in the Establishment of Environmental Cancer." Invitation of Dr. Robert Briggs.

March 24, 1955 - Guest Lecturer - Military Preventive Medicine Course at Army Medical Service Graduate School, Washington, D. C. Title of Lecture: "Industrial Cancer". Invitation by Col. Charles H. Moseley, M.C. Dir. Div. Preventive Medicine.

April 1, 1955 - Principal Guest Speaker, Industrial Medical Association, Kansas City, Missouri. Address: "Industry Vs. Cancer." Invitation by Dr. Terry E. Lilly, Jr., President, above Association.

March 2, 1955 - Memorial Center Lecture titled:-"Carcinogenic Hazards in Modern Industrialized Societies." Invitation of Dr. Frederick S. Philips, Chairman Seminar Committee, Memorial Cancer Center, New York.

May 3, 1955 - Lecture to Cancer Control Class on "Environmental Carcinogens." Yale University, Department Public Health, New Haven, Invitation by Dr. Edward M. Cohart.

May 23, 1955 - Address - "Causal and Preventive Aspects of Environmental Cancer", Minnesota State Medical Society and Minnesota Division of the American Cancer Society, Minneapolis, at the invitation of Mr. Allen Stone, Exec. Dir. Minnesota Div. ACS and Dr. Wangensteen, Program Director.

PROJECT REPORT FORM

10. OADR-209
SERIAL NO.

16. ADDRESSES (cont)

June 3, 1955 - Address to Session on Legal Medicine, Atlantic City, Annual Meeting of the American Medical Association on the subject:-"Trauma and Cancer." Invitation by Dr. Richard Ford.

September 16, 1955 - Conference of Field Investigators, Field Studies Section, NCI. Bldg. T-6, NIH. Guest Speaker at 1-week conference on Sept.16- Title:-"Recent Developments in Environmental Carcinogenesis." Chairman:- Dr. S. C. Ingraham. Invitation by Dr. R. Kaiser.

November 6, 1955 - Presented Guest Lecture at the Annual Meeting of the American Society for the Study of Arteriosclerosis, Hotel Sheraton, Chicago, Ill. "Arteriosclerosis and Cancer: A Study in Relationships. Invitation of Dr. Chas. F. Wilkinson, Jr. Chairman, Program Committee

November 18, 1955 - Presented an informal talk on the subject of "Potential Industrial Carcinogenic Hazards" during the luncheon meeting of executives of the Arthur D. Little Corporation, Cambridge, Mass. at the invitation of Dr. Charles Kensler.

PROJECT REPORT FORM

1. Cancer — INSTITUTE
2. Office Assoc. Dir. in Chg. of Research — LABORATORY OR BRANCH
3. Environmental Cancer Section
4. — LOCATION(IF OTHER THAN BETHESDA)
5. OADR-210a — SERIAL NO.

6. Studies on Occupational and Environmental Respiratory Cancer Hazards Caused by the Inhalation of Carbonaceous Air Pollutants (Coal Tar, Petroleum Asphalt, Cutting Oil, Coffee Roast Soot).

7. W. C. Hueper

8. Wm. W. Payne

9. PROJECT DESCRIPTION

Objectives: The alarming rise of lung cancers during recent decades has directed attention to combustion and oxidation products of various types of carbonaceous matter (coal soot, coal tar, dust and fumes, carbon blacks, petroleum asphalt dust and fumes, cutting oil mists, diesel and gasoline engine exhausts, tarry fumes from tobacco products, sooty material from roasted coffee, oxidation products of evaporated gasoline) which pollute to an increasing degree the occupational and general human environment. The study of coal tar and petroleum asphalt fumes, cutting oil mists, and coffee roast soot was chosen, since the first three mentioned agents are potentially important occupational respiratory carcinogens which have attracted little attention by other investigators, while the fourth was selected because it might play a significant role in accounting for the astonishly high lung and larynx cancer morbidity and mortality rates in New Orleans where coffee roasting plants and air pollution caused by their effluents are environmentally unique features.

Methods Employed: a) Coke oven tar and petroleum roofing asphalt are heated by an electric device within exposure chambers to 275° C. and 320° C., respectively. Large amounts of fumes are thereby given off by these materials.

The temperature within the chambers is kept at a level of about 76°-78° F. by the introduction of cooled air generated by an air conditioning unit. Rats and guinea pigs are exposed to the fumes for 8 hours daily about five times per week.

The carcinogenicity of the coal tar used was established by the development of carcinomas of the skin in all survivors of a series of 25 C57 black mice painted for 6 months with this coal tar and by the demonstration of sarcomas in the thighs of mice intramuscularly injected with the extract of the filter pad in which the fumes which had passed the chamber had been absorbed. Similar tests were recently started with the petroleum asphalt used.

PROJECT REPORT FORM(cont)

OADR-210 a
SERIAL NO.

PUBLICATIONS:

Hueper, W. C., An analysis of the environmental causes of lung cancer, p. 149-179, Proc. Mid-Year Meeting, 1954, Am. Pharmaceut. Manuf. Assoc. New York, 1955.

Hueper, W. C., Lung cancers and their causes. CA-A Bulletin of Cancer Progress. 5:95-100, 1955.

Hueper, W. C., Environmental Lung Cancer. Proc. First Canadian Cancer Research Conference, 1954, National Cancer Institute of Canada. Academic Press, Inc., New York, 1955, pp. 186-236.

Hueper, W. C., Environmental Causes of Cancer of the Lung Other than Tobacco Smoke. Dis. Chest. In Press.

Hueper, W. C., A Quest into the environmental causes of cancer of the lung. Publ. Health Service Publ. No. 452, 1955.

Hueper, W. C., Environmental cancer of the lung. Acta Unio Internat. Contra Cancrum. In Press.

HONORS AND AWARDS RELATING TO THIS PROJECT:

Jan. 28-29, 1955 - Special Conference on Lung Cancer and Heart Disease, Princeton Inn, N. J. Sponsored by the American Cancer Society. "Environmental Causes of Cancer of the Lung". Invitation of Dr. Harry M. Weaver.

March 15, 1955 - Panel Discussion on Smoking and Lung Cancer. Clinical Center Auditorium, NIH, "Environmental, Occupational and Industrial Cancer."

March 21, 1955 - Seminar- Talk to Chemistry Department, The Catholic University of America, Washington, D. C. "Smoking and Lung Cancer." Invitation of Dr. J. T. Vanderslice.

June 2, 1955 - Address - "Environmental Causes of Cancer of the Lung Other Than Tobacco Smoke" . Symposium of American College of Chest Physicians on "What Is Causing the Increase of Cancer of the Lung", Hotel Ambassador, Atlantic City, N. J. Inv. by Dr. Edgar Mayer.

October 14, 1955 - By invitation of Mr. C. R. Houchins, Secy. Assoc. Physicians and Surgeons of the P. R.R. "Industrial and Industry-Related Lung Cancer Hazards". Clinical Center Auditorium, Association of Physicians and Surgeons of the Pennsylvania Railroad.

12/22/55

PROJECT REPORT FORM

1 National Cancer Institute 2. Office of the Assoc. Director in Chg. Res.

3 Environmental Cancer Section 4. 5. OADR-210(b)
LOCATION(IF OTHER THAN BETHESDA) SERIAL NO.

6 PROJECT:-Analysis of material retained by dusting chamber exhaust filters

7 PRINCIPAL INVESTIGATOR:- H. J. Cahnmann

8 None
OTHER INVESTIGATORS

9 PROJECT DESCRIPTION

Objectives:- The objective of this investigation was to determine whether heating of tar in a closed chamber under conditions simulating those prevailing in tar processing industries, will contaminate the air passing through the chamber with appreciable amounts of polynuclear aromatic hydrocarbons, particularly those in the "carcinogenic range" (4 - 6 rings).

Methods employed: The cellulose filters received from Dr. Hueper and Mr. Payne contained a large amount of very dark brown, sticky material. This material was fractionated by solvent extraction, followed by chromatographies on activated alumina and on partly deactivated silica gel. The fractions obtained were evaluated spectrophotometrically.

Major findings: Although all fractions obtained still represent mixtures of compounds, no attempts were made to break them down into individual compounds which would necessitate a series of additional chromatographic fractionations and spectrophotometric evaluations. The spectra obtained from the still rather crude fractions already permit the following conclusion:- - Polycyclic aromatic hydrocarbons are present in considerable quantities. The ones of lower molecular weight (2 and 3 rings) are by far predominant, but higher ring systems could also be detected.

Significance to cancer research:) cf. Dr. Hueper's report
Proposed course of project:)

1. RESEARCH(Budget Activity)

) ENTRIES FOR ITEMS 12, 13, 14, 15 and 16.

PROJECT REPORT FORM 12/22/55

1. Cancer INSTITUTE
2. Office Assoc. Director in Chg. Research LABORATORY OR BRANCH
3. Environmental Cancer Section SECTION OR SERVICE
4. LOCATION (IF OTHER THAN BETHESDA)
5. ADR-211 SERIAL NO.

6. Evaluation of various adsorbents elution methods for the chromatographic fractionation of polynuclear aromatic hydrocarbons. Project A
PROJECT TITLE

7. H. J. Cahnmann
PRINCIPAL INVESTIGATOR(S)

8. None
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: A successful and efficient chromatographic resolution of a complex hydrocarbon mixture depends largely on the proper choice of the adsorbent and elution method used. In order to make a rational experimental approach in future investigations (cf. projects B and C) it was necessary to evaluate a number of adsorbents and elution methods.

Methods employed: Test substances (either benzo(a)pyrene or binary mixtures of hydrocarbons) were chromatographed under various conditions, and the chromatographic behavior of the test substance under these conditions was studied. In a first series of experiments a large number of adsorbents were compared with each other under otherwise identical conditions. In a second series of experiments a comparative study of two different elution methods was made with a given adsorbent and a given solute. In a third series of experiments the influence of a gradual and controlled deactivation of activated alumina as well as of silica gel on the chromatographic behavior of the solute was recorded. In a fourth series of experiments the influence of the activation temperature on the performance of silica gel as an adsorbent was investigated. In all series the behavior of the solute (width, sharpness, rate of movement, etc. of the chromatographic zones, irreversible adsorption of the solute, degree of separation of a solute mixture, etc.) was recorded.

Major findings: Different brands of activated alumina behave very differently. One brand appears to be particularly well suited for the separation of polynuclear aromatic hydrocarbons. This is an alkaline fine grained material. Alkaline aluminas give narrower and sharper chromatographic hydrocarbon zones than acid or neutral aluminas. It would be desirable to use a still finer grained alumina than the one at hand if chromatographic separations are to be performed on a microscale. Silica gel (where also the finer grain sizes are more effective than the coarser ones) is superior to activated alumina in many instances. Other adsorbents tried seem to be less effective than alumina or silica gel although the limited number of experiments performed

PROJECT REPORT FORM (cont)

10. CADR-211
SERIAL NO.

9. PROJECT DESCRIPTION (cont)

Project A (cont) Major findings (cont)

do not permit to draw final conclusions. The use of partly deactivated alumina or silica gel (obtained through controlled deactivation with water) offers in many instances considerable advantages over the use of fully activated adsorbents. Heating to 500°C. (as frequently recommended) transforms silica gel into a very poor adsorbent, no matter whether the heated silica gel is used as such or after partial deactivation. Activation at 150-200°C. yields an excellent adsorbent.

Significance to cancer research: Most analytical investigations of carcinogens of the polynuclear aromatic type present in complex mixtures are based on chromatographic procedures. It is, therefore, important to study the optimal conditions for such chromatographic fractionations, particularly when trace amounts of carcinogens are to be detected (cf. project B). No comprehensive comparative studies of this sort have yet been published in the field of polynuclear aromatic hydrocarbons. The preliminary results obtained so far have already been of considerable help in various investigations in our laboratory (cf. projects B and C). Particularly the use of partly deactivated silica gel permitted separations which were hardly possible with other adsorbents.

Proposed course of project: It is intended to publish a short note on the use of partly deactivated silica gel for chromatographic fractionations in general and for the separation of polynuclear aromatic hydrocarbons in particular. This method has only once been hinted at in the literature, but never has been described in detail nor ever been used in chromatographic practice. A more detailed and more complete treatment of this subject would necessitate considerably more experimental work which was not possible so far due to pressure of time and to lack of manpower. This holds also true for the other preliminary findings mentioned above which cannot be published separately without a number of additional experiments. Some of them may be included in a publication resulting from project B.

11. Research
BUDGET ACTIVITY

NO ENTRIES FOR ITEMS 12, 13, 14, 15 and 16.

12/22/55

PROJECT REPORT FORM

1. Cancer — 2. Office of Assoc. Director in Chg. Research
INSTITUTE — LABORATORY OR BRANCH

3. Environmental Cancer Section — 4. _____ — 5. OADR-212
SECTION OR SERVICE — LOCATION (IF OTHER THAN BETHESDA) — SERIAL NO.

6. Studies on Possible Cancer Hazards Related to the Use of Food Dyes

7. Dr. Paul L. Malloy

8. Elizabeth J. Lethco

9. PROJECT DESCRIPTION

Objective: Hypothetical metabolites of several certified food dyes are known to be carcinogenic to man. This project is designed to clarify the metabolism of two such dyes - Yellow AB and Yellow OB (F.D. and C. Yellow #3 and #4).

Methods Employed:

1. The dye, Yellow AB, was purified by repeated crystallizations from butyl alcohol and subsequently examined for traces of free β-naphthylamine. The recrystallizations were repeated until no free amine could be detected.

2. Several hypothetical metabolites of the dye have been synthesized and studied chromatographically and spectrophotometrically to serve as reference compounds and as guides in the isolation of the actual metabolites.

3. The purified dye has been administered to test subjects in three ways:

a) Massive doses have been fed to dogs, both "single-shot" and also continually for several days.
b) Varied doses have been administered to dogs by surgical implantation, usually by insertion into isolated segments of the gastro-intestinal tract. (cf. Report of Cancer Surgery Division, Dr. R. R. Smith and D. Cole.)
c) Quantities of the dye somewhat in excess of the amounts normally ingested in foods have been ingested by humans. In each case, the excreta have been collected and examined for the presence of these metabolites for which the chromatographic and spectrophotometric properties have been established.

In addition, advantage has been taken of the large scale administration of the dye which consists of consumption of the dye in normal foods by the public at large. Several hundred gallons of urine were collected from the public at large and concentrated. This concentrate provides a fourth test object.

PROJECT REPORT FORM(cont)

10. OADR-212
SERIAL NO.

9. PROJECT DESCRIPTION(cont)

Methods Employed(cont):

In the clinical phases of these investigations, members of the Surgery Branch, NCI (Drs. R. R. Smith and Jack Waite)are cooperating.

Major Findings:

Results thus far obtained are inconclusive but suggest the presence of a carcinogenic metabolite of the dye, Yellow AB.

Significance to Cancer Research:

If the metabolism of food dyes produces carcinogenic substances, then the removal of these dyes would protect the general public from a serious cancer hazard.

11. BUDGET ACTIVITY -- RESEARCH

NO ENTRIES FOR ITEMS 12, 13, 14, 15 and 16.

1. National Cancer Institute — INSTITUTE
2. Office of the Assoc. Dir. — LABORATORY OR BRANCH
3. Comparative Pathology Section — SECTION OR SERVICE
4. -------
5. NCI - 215 — SERIAL NO.

6. Project Title: A study of the histopathological characteristics of experimentally induced and naturally occurring tumors in laboratory, domestic, and wild animals.

7. Principal Investigator: Dr. W. H. Eyestone

8. Other Investigators: Dr. Anton M. Allen

9. Project Description:

Objectives: To be well informed through experience, concerning the histopathologic characteristics of these tissues, to plan experiments and/or cooperate with other scientists in the interpretation of such data.

Methods employed: A continuing survey of the histopathological characteristics of tumors in domestic and wild animals is made by obtaining these tissues from the National Zoological Park, from the NIH Animal Colony, and from practicing veterinarians throughout the U.S.A. Through contacts with scientists in the Cancer Institute, special interest fields are selected and experiments are planned with these scientists so that maximum benefit may be obtained from the experimental material for pathological evaluation.

Major findings: Examined and described over 325 autopsies and/or biopsies of tumor material from domestic and wild animals during 1955. A summary of these findings indicates an approximate incidence of 2.5% tumors in aged captive wild animals, among which no tumors of primates were observed. There is a relatively high incidence of carcinoma in old dogs, particularly carcinoma of the breast.

A functional adrenal-cortical carcinoma in Osborne-Mendel rats, the tissue of which is transplantable and functional (causes atrophy of host adrenals), was reported in the literature. (J.N.C.I., Dec. 1955)

Significance to Cancer Research: A broad background of knowledge of the histologic characteristics of tissues from experimental animals is used to interpret data, and also to assist scientists not having specialized training to analyze this aspect of their results.

Proposed course of project: Continuation.

10. NCI-215
SERIAL NO.

11. BUDGET ACTIVITY:

RESEARCH /7/ ADMINISTRATION /7/

REVIEW & APPROVAL /7/ TECHNICAL ASSISTANCE /7/

12. ------

13. ------

15. Publications:

Mulay, A. S. and Eyestone, W. H.: Transplantable Adrenocortical Adenocarcinomas in Osborne-Mendel Rats Fed a Carcinogenic Diet. J. Nat. Can. Inst., 16:3, December 1955.

16. ------

1. National Cancer Institute	2. Office of the Associate Director	3.	4. ------	5. NCI-216
INSTITUTE	LABORATORY OR BRANCH			SERIAL NO.
Comparative Pathology Section				
SECTION OR SERVICE				

Project Title: A study of the naturally occurring diseases of laboratory animals.

Principal Investigator: Dr. Robert T. Habermann

Other Investigators: Mr. Fletcher P. Williams, Jr.

Project Description:

Objectives: The objectives of the project are to develop healthy, vigorous, "disease-free" animals for research workers at the N.I.H.; conduct research work on bacterial, viral, mycotic, neoplastic, degenerative, and parasitic diseases to enable investigators to distinguish between the pathology produced experimentally from that produced by the naturally occurring diseases in N.I.H. animals; to develop effective methods for the control or prevention of these diseases; and to develop technics for the early recognition of an outbreak of disease in the animal colonies.

Methods employed: (1) Various chemical substances are painted on the floor, cages, and racks in animal rooms to determine the efficacy of the chemicals to control vermin. (2) Various chemical substances are dusted on infected laboratory animals to determine the efficacy of the chemicals to control external parasites. (3) Various chemical substances are admixed in ground animal feeds to determine the efficacy of the chemicals in the control of internal parasites. (4) Various chemical substances are admixed in ground animal feeds to determine the efficacy of the chemicals in the treatment and control of diseases of laboratory animals. (5) Various methods of sanitation and of the care of laboratory animals are employed to determine the efficacy of these methods for controlling diseases. (6) Various methods and media for the isolation of the cause of disease are used to determine efficacy of methods for the isolation of organisms. (7) Daily inspections of animals are conducted by attendants to remove sick and unhealthy animals so that the sources of infection are removed and a healthier colony of laboratory animals is obtained. (8) Daily parasitic, bacteriologic, and histopathologic examinations are made of sick, unhealthy, and aged animals to determine the incidence of diseases and to detect any new disease or spread of disease in the animal colonies.

Major findings: The major findings of this project during the past year have been (1) the use of aureomycin as a possible control of respiratory and middle ear infections in rats; (2) the use of a saturated solution of sulfaguanadine in the drinking water of rabbits in the animal colonies for the control of coccidiosis; (3) the determination of the absence of sarcosporidiosis and leptospirosis in mice, of the absence of salivary gland disease in guinea pigs, and extremely low incidence of mycotic diseases in laboratory animals; and (4) the determination of high incidence (40 percent) of Trichosomoides crassicauda in O.M. strain of rats.

NCI-216
SERIAL NO.

Significance to Cancer Research: The development of healthier laboratory animals so that the experimental results are more reliable, that less animals are needed to obtain dependable experimental results, and that the cost of conducting experiments is reduced.

Proposed Course of Project: A considerable portion of the next calendar year will be devoted to the control, treatment, and elimination of diseases from the laboratory animals, to the study and treatment of snuffles in rabbits, and to the histopathologic study of distemper, giant cell pneumonia, and leptospirosis in animals.

11. BUDGET ACTIVITY:

RESEARCH ☐ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

12. ------

13. ------

15. Publications:

Menges, Robert W., Robert T. Habermann, and Howard G. Strains: A Distemper-like disease in Raccoons and Isolation of Histoplasma capsulatum and Haplosporangium parvum. Trans. Acad. Sci., 58:1, 1955.

Menges, Robert W. and Robert T. Habermann: Experimental Avian Histoplasmosis. Am. J. Vet. Res., 16:59, 314-320, 1955.

Congdon, Charles C., Fletcher P. Williams, Jr., Robert T. Habermann, and Egon Lorenz: The Histopathology of Bacterial Infection in Irradiated Mice. J. Nat. Cancer Inst., 15:4, February 1955.

16. ------

PROJECT REPORT FORM

1. NCI — INSTITUTE
2. OADR — LABORATORY OR BRANCH
3. Clinical Pharm. & Exper. Therapeutics Section — SECTION OR SERVICE
4. None — LOCATION (IF OTHER THAN BETHESDA)
5. NCI-220 — SERIAL NO.

Research in the Chemical and Physico-chemical Properties of Antitumor Agents
PROJECT TITLE

Dr. Ti Li Loo
PRINCIPAL INVESTIGATOR(S)

None
OTHER INVESTIGATORS

PROJECT DESCRIPTION

Project: Research in the Chemical and Physico-chemical Properties of Antitumor Agents

Objectives: To study the chemical and physico-chemical properties of antitumor agents currently in use in order to enquire into their mode of action.

Methods employed: The structure of each antitumor agent will be investigated by standard physico-chemical methods. The chemical changes that a drug undergoes, such as hydrolysis, under physiological conditions will be studied kinetically. The interaction of each agent with such cell components as amino acids, proteins, etc. will be followed chemically as well as physico-chemically.

Major findings: None at the present as this project has not yet been initiated.

Significance to CANCER Research: Before the study of the mechanism of action of the antitumor agents is attempted, it is clearly essential that their chemical and physico-chemical properties be well understood. Of primary importance, for instance, will be the stability of the agent. If it is unstable, one is at once concerned with the cause of its instability as well as the exact nature of the transformations it undergoes under the circumstances. Further, the perplexing complexity of the problem of the mechanism of action of the antitumor agents dictates that, as a first approach, advantage must be taken of the employment of a system which simulates the physiological environment in which the drug exerts its action but in a much

simplified fashion. As an example, the information gathered from the research in the interaction between an antitumor agent and a single protein would perhaps be expected to be reasonably transposable to the cellular scale.

Proposed course of project:

1. The properties and structural features of 6-mercaptopurine will be studied.

2. The chemical behavior of 6-mercaptopurine, especially its reduction, will be investigated, since the last mentioned reaction constitutes the first step in the newly developed colorimetric determination of 6-mercaptopurine.

3. The hydrolysis of N,N',N" - triethylene thiophosphoramide under a variety of conditions will be studied kinetically in order to gain some insight into its mode of action.

4. The chemical properties of any agent on which the attentio of our clinical investigators is focused will be likewise studied as the occasion arises.

5. The interaction of the antitumor agents with proteins, especially nucleoproteins will be followed by suitable means.

PROJECT REPORT FORM (Cont'd)

NCI - 220
SERIAL NO.

BUDGET ACTIVITY:

RESEARCH ☐ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 or 1957

IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

NO ENTRIES FOR ITEMS 14, 15, & 16

PROJECT REPORT FORM

1. NCI — INSTITUTE
2. OADR — LABORATORY OR BRANCH
3. Clinical Pharm. & Exper. Therapeutics Section — SECTION OR SERVICE
4. None — LOCATION (IF OTHER THAN BETHESDA)
5. NCI-221(C)

6. Pharmacology of Amethopterin
PROJECT TITLE

7. Marian V. Freeman, Ph. D.
PRINCIPAL INVESTIGATOR(S)

8. C. G. Zubrod, M.D.
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Project: Pharmacology of Amethopterin

Objectives: To determine the pharmacology of amethopterin and to compare the various aspects of it in:

a. Animals responding to the drug

b. in patients responding

c. not responding and

d. in those relapsing while on drug.

Methods employed: Various chemical methods are being used or adapted for use in this project. Final measurements are fluorimetric measurements.

Major Findings:

1. The ability of amethopterin to fluoresce has been adapted to its determinations in blood and urine.

2. Using this method, some aspects of its pharmacology have been examined. It has been found that the drug is rapidly absorbed from the G.I. tract, that plasma concentrations are not measurable 2 hours after a 2.5 mg. dose, that the material rapidly appears in the urine and that its volume of distribution indicates it to be present in extracellular fluid.

PROJECT REPORT FORM (Cont'd)

Significance to CANCER Research: It is hoped that in determining the path of this drug in patients that some light may be thrown on its more effective use and on its inability to act in some cases.

Proposed course of project: It is proposed:

1. To extend the method for measuring amethopterin to other body tissues and to the determination of its metabolites.

2. To ascertain its distribution in blood and other components of the body as well as its form in the urine.

3. To compare its pharmacology in:

   a. animals responding to the drug

   b. in patients responding and

   c. not responding and in

   d. those relapsing while on the drug.

PROJECT REPORT FORM (Cont'd)

10. NCI - 221(C)
SERIAL NO.

11. _____
BUDGET ACTIVITY:

RESEARCH	☐	ADMINISTRATION	☐
REVIEW & APPROVAL	☐	TECHNICAL ASSISTANCE	☐

12. _____
COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 or 1957

13. _____
IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

NO ENTRIES FOR ITEMS 14, 15, & 16

PROJECT REPORT FORM

1. NCI
INSTITUTE

2. CADR
LABORATORY OR BRANCH

Clinical Pharm. & Exper.
3. Therapeutics Section
SECTION OR SERVICE

4. None
LOCATION (IF OTHER THAN BETHESDA)

5. NCI-222

Some of the Pharmacological Properties of Tumor Tissue
PROJECT TITLE

Marian V. Freeman, Ph. D.
PRINCIPAL INVESTIGATOR(S)

C. G. Zubrod, M.D.
OTHER INVESTIGATORS

PROJECT DESCRIPTION

Project: Some of the Pharmacological Properties of Tumor Tissue

Objectives: To learn something of the pharmacological behavior of tumor tissue in an effort to understand it and how to alter it.

Methods employed: This study has been started with the ability of leukemic cells to take up pharmacologic agents. It is involving the separation of white blood cells by sedimentation of the blood with macromolecules, slow centrifugation to separate white blood cells from red blood cells and plasma, then separation of one type cell from another by centrifugation through different density albumin solutions. It also involves standard chemical procedures.

Major findings: That sulfonamide is taken up by leukemic white blood cells in proportion to the number of cells present and that this is quantitatively similar to the uptake of sulfonamide by red blood cells.

Significance to CANCER Research: It is thought that an understanding of the basic ability of tumor tissue to handle pharmacological agents will aid in the development of a rational approach to their destruction.

Proposed Course of Project:

1. To determine the ability of other tumor tissue to take up the drug.
2. To determine the ability of the various type white blood cells to take up this drug.
3. To determine the ability of this tumor tissue to handle other pharmacological agents. This will ultimately include uptake binding, distribution, and disposition of drugs by these tissues.

PROJECT REPORT FORM (Cont'd)

10. NCI-222
SERIAL NO.

11. BUDGET ACTIVITY:

RESEARCH	☐	ADMINISTRATION	☐
REVIEW & APPROVAL	☑	TECHNICAL ASSISTANCE	☐

12. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 1957

13. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

NO ENTRIES FOR ITEMS 14, 15, & 16

PROJECT REPORT FORM

1. NCI
INSTITUTE

2. OADR
LABORATORY OR BRANCH

3. Clinical Pharm. & Exper. Therapeutics Section
SECTION OR SERVICE

4. None
LOCATION (IF OTHER THAN BETHESDA)

5. NCI-223

Penetration of Anti-tumor Drugs into the Central Nervous System
PROJECT TITLE

Dr. David P. Rall, Dr. C. G. Zubrod
PRINCIPAL INVESTIGATOR(S)

None
OTHER INVESTIGATORS

PROJECT DESCRIPTION

Project: Penetration of Anti-tumor Drugs into the Central Nervous System

Objectives: The objectives of this project are to quantitate the penetration of certain anti-tumor drugs into the central nervous system (CNS) after parenteral administration, and to attempt to elucidate some of the factors influencing the relationship between dose of drug, plasma level, and concentration of drug in the CNS.

Methods employed: Standard pharmacologic technics will be used as the basis of these studies.

Major findings: As this is a new project, there are as yet no major findings.

Significance to CANCER Research: Tumors, both primary and metastatic, frequently develop within the central nervous system. Little information is available in the published literature concerning the penetration of anti-tumor drugs into the CNS. Basic research on the concentration of anti-tumor drugs within the CNS is necessary for the rational use of these agents in the treatment of patients with tumors thus located.

Proposed course of project: The following lines of investigation are planned:

1. Investigation of the relationship between central nervous system tissue levels and cerebrospinal fluid levels after drug administration.

PROJECT REPORT FORM (Cont'd)

2. Development of methods for repeatedly sampling cerebrospinal fluid without disturbing cerebrospinal fluid dynamics, and thereby possibly influencing the penetration into the CN of the drug under study.

3. Exploration of the relationship between plasma drug levels and CNS drug levels after varying dosage under both steady and unsteady state conditions.

4. Investigation of the influence of injury, inflammation, and pharmacologically active agents on the penetration of anti-tumor drugs into the central nervous system.

The above initial experiments will be performed using the dog as the test animal. As the project develops it will be extended to include certain similar observations in patients with suitable tumors.

PROJECT REPORT FORM (Cont'd)

0. NCI - 223
SERIAL NO.

1. BUDGET ACTIVITY:

RESEARCH	☐	ADMINISTRATION	☐
REVIEW & APPROVAL	☐	TECHNICAL ASSISTANCE	☐

2. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 or 1957

3. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

NO ENTRIES FOR ITEMS 14, 15, & 16

PROJECT REPORT FORM

1. NCI
INSTITUTE

2. OADR
LABORATORY OR BRANCH

3. Clinical Pharm. & Exper. Therapeutics Section
SECTION OR SERVICE

4. None
LOCATION (IF OTHER THAN BETHESDA)

5. NCI-224(C)

6. Patheogenisis of Fever in Cancer Patients
PROJECT TITLE

7. Dr. David P. Rall
PRINCIPAL INVESTIGATOR(S)

8. None
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Project: Patheogenisis of Fever in Cancer Patients

Objectives: To determine if there is a circulating pyrogen in the blood of cancer patients with bacterial or viral infections and with febrile episodes of unknown etiology.

Methods: Blood samples from normal and febrile patients will be assayed for pyrogenicity by injecting them, in toto or after fractionation, into rabbits. The febrile response of the rabbit will indicate the pyrogen present. Characterization of the pyrogen will be done by comparing the response in fresh rabbits and those previously made tolerant to bacterial pyrogen, by determing the heat lability of the pyrogen in blood, by determining the time course of the fever and the associated circulating leucocyte changes.

Major findings: This is a new project; very preliminary results indicate that blood from febrile patients may contain a pyrogen in amounts adequate to be detected by the rabbit assay.

Significance to CANCER Research: Fever, of known or unknown etiology, is a constant problem in patients with cancer. Any information on its cause will aid in the palliatine treatment of these patients. Of particular interest is whether leukemic white cells contains pyrogen, since it has been reported that normal white cells are pyrogenic (Bennett & Beeson).

Proposed course of project: First the pyrogenicity of blood from febrile patients will be confirmed. If so, attempts will be made to characterize this pyrogen, again with particular reference to whether or not the leucocytes are involved.

PROJECT REPORT FORM (Cont'd)

10. NCI - 224 (C)
SERIAL NO.

11. BUDGET ACTIVITY:

RESEARCH ☐ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

12. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 or 19

13. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

NO ENTRIES FOR ITEMS 14, 15, & 16

PROJECT REPORT FORM

1. N.C.I. — INSTITUTE
2. O.A.D.R. — LABORATORY OR BRANCH
3. Clinical Pharmacology and Experimental Therapeutics — SECTION OR SERVICE
4. — LOCATION (IF OTHER THAN BETHESDA)
5. NCI-225(C) — SERIAL NO.

6. Studies of the pharmacology of anti-tumor agents. — PROJECT TITLE

7. Dr. P. T. Condit, Dr. M. V. Freeman, Dr. M. Lane, Dr. T. L. Loo, Dr. D. P. Rall and Dr. C. G. Zubrod. — PRINCIPAL INVESTIGATOR(S)

8. — OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: The immediate object of this project is to determine the total pharmacology of drugs actually and potentially useful in the treatment of patients with neoplastic disease, and to acquire a better understanding of their mode of action. Ultimately the goal is to develop more effective drugs for the control of human cancer.

Methods employed: Standard analytic and pharmacologic techniques will be the basis for these studies. New methods will be developed as required by the problems under investigation.

Patient material: Patients with suitable neoplastic disease will participate in these studies.

Major findings: Since the section has just been organized, there are no results to report. Previous work by the several investigators is detailed in their individual project reports. (Dr. Condit, Dr. Freeman and Dr. Lane).

Significance to Cancer Research: The chemotherapy of cancer is still in its infancy, and the mechanism of action of the current anti-tumor agents remains obscure. These studies are designed to obtain information regarding desirable drug dosage for man, methods of administration and signs of toxicity. The absorption, distribution and metabolic fate of these drugs are of importance in evaluating their clinical effects. It is hoped that such pharmacologic studies of anti-tumor agents will further the present understanding of their mode of action, and thus furnish some guide to the development of more effective agents.

PROJECT REPORT FORM (cont'd)

Proposed course of project: On the basis of the chemical, physical and biological characteristics of each anti-tumc drug, attempts will be made to devise method for the measurement of the particular agent and its derivatives in biologic materials. The pharmacology of each drug will then be stud in experimental animals and later in patients. As the work on a specific drug becomes a major study, it will be reported under a separate project.

PROJECT REPORT FORM (Cont'd)

NCI - 225(C)
SERIAL NO.

BUDGET ACTIVITY:

RESEARCH	[X]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	TECHNICAL ASSISTANCE	[ ]

1.

COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 or 1957.

1.

IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

N entries for items 14, 15 and 16.

PROJECT REPORT FORM

1 N.C.I. — INSTITUTE
2. O.A.D.R. — LABORATORY OR BRANCH

3 Clinical Pharmacology and Experimental Therapeutics — SECTION OR SERVICE
4. — LOCATION (IF OTHER THAN BETHESDA)
5. NCI-226C — SERIAL NO.

6 Pharmacology of the Folic Acid Antagonists.
PROJECT TITLE

7 Paul T. Condit
PRINCIPAL INVESTIGATOR(S)

8 Emil Frei, III and Abraham Goldin
OTHER INVESTIGATORS

9 PROJECT DESCRIPTION

Objectives: The goal of this project is to find out more about the mechanism of action of the folic acid (PGA) antagonist. In addition to problems of dosage regimens, the study was motivated by two problems which frequently arise during the use of these drugs in the treatment of acute leukemia:

(1) Why do some patients respond to these drugs while others do not?

(2) Why do all patients ultimately become refractory to further treatment?

Methods employed: PGA (or citrovorum factor (CF)) together with inulin is administered to patients by intravenous infusion, and blood and urine samples collected over a 24 hour period. From the concentrations of PGA, CF and inulin in the various samples, the volume of the extracellular fluid (ECF), the glomerular filtration rate, the distribution of PGA in the various fluid compartments, the rates of excretion and extra-renal uptake of PGA and the urinary excretion of CF can be calculated. A comparison of such studies performed before and after the patient received aminopterin, provides some information about the site and mechanism of action of the PGA antagonists.

Patient studies are supplemented by animal experiments carried out in collaboration with Dr. A. Goldin of the Laboratory of Chemical Pharmacology.

Patient Material: Patients studied at the Baltimore USPHS Hospital: Normal 2, chronic lymphocytic leukemia 2, chronic myelocytic leukemia 1, carcinoma antrum 1. Patients studied at The Johns Hopkins Hospital: achromegaly 1, Laennec's cirrhosis 2, cerebrovascular accident (old) 1.

PROJECT REPORT FORM (cont'd)

Major Findings: A simplified technique has been developed for measuring E(volume using inulin.

PGA is readily taken up by the cells of the body and subsequent conversion or utilization occurs intracellularly. The system whi utilizes PGA can be overloaded by large doses of PGA, and can also be inhibited by aminopterin. The system may be less effective in patients wi chronic leukemia.

The conversion of PGA to CF (as indicated by urinary CF excretion) is al inhibited by aminopterin, but accounts for only a small amount of the PG retained by the body. Following the administration of PGA to mice, total liver CF increases to a maximum in one hour, and then returns to pre-trea ment levels by eight hours. The magnitude and duration of these changes mice suggest that in man this process alone would be insufficient to account for all of the PGA retained.

CF is taken up by the body cells more rapidly than is PGA, but, unlike P(, the uptake is unaffected by aminopterin.

Significance to Cancer Research: It is felt that a detailed knowledge of e total pharmacology of the PGA antagonist is important, not because these drugs ar in themselves essential, but because they are representatives of the lar class of antimetabolite drugs. The general principles of the clinical u of the PGA antagonists, which should result from this study, may well be applicable to other antimetabolites with clinical usefulness. Such prin ciples are of particular interest in the general field of cancer chemotherapy, because many of the compounds suggested for clinical trial are antimetabolites.

The clinical usefulness of the PGA antagonists is probably less importan than the role they can play in elucidating the abnormalities which are known to exist in PGA metabolism in human leukemia. The existence of th e drugs provides a unique opportunity to study the basic biochemical differences between patients with leukemia and normal subjects.

Proposed Course of Project: It is planned to extend these investigations i the directions suggested below:

(1). Because of its importance in planning dosage regimens with the PGA antagonists, the duration of action of thes drugs will be studied in both man and animals. Patients will be admitte for detailed studies of the recovery from the effects of methotrexate. Measurement of total CF in mouse liver at intervals following a dose of methotrexate is nearly complete. These measurements will be extended to different dosage schedules in an attempt to determine the most effective way to use this drug.

(2). The changes in total CF in mouse leukem L1210 which occur after methotrexate will be determined. The goal of s h

determinations is the correlation of metabolite levels in the host and in the tumor with dosage schedules, so that ultimately a rational basis for the use of these drugs can be obtained.

(3). Although most of the work on the pharmacology of the PGA antagonists which has been done and which is planned for this project has been directed primarily at the metabolites (PGA and CF), it is also desirable to do some studies on the distribution and fate of methotrexate itself. The general methods developed during the study of PGA will be used.

(4). Plans have been completed, in collaboration with Dr. E. Frei of the Leukemia Section, to study a few patients with acute leukemia to find out if differences in PGA metabolism in the host can be detected by the methods developed by this project. An attempt will be made to correlate PGA metabolism with the clinical response of the patient to methotrexate.

(5). The amounts of PGA and of CF in different kinds of human leukocytes will be measured. Correlations with the degree of maturity of the cells and with the clinical response of the patient to the PGA antagonists will be attempted.

PROJECT REPORT FORM (Cont')

10. NCI-226 (C)
SERIAL NO.

11. BUDGET ACTIVITY:

RESEARCH	[X]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	TECHNICAL ASSISTANCE	[ ]

12. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 or 1957.

13. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

No entries for items 14, 15 and 16.

PROJECT REPORT FORM

1. N.C.I. — INSTITUTE
2. O.A.D.R. — LABORATORY OR BRANCH
3. Clinical Pharmacology and Experimental Therapeutics — SECTION OR SERVICE
4. — LOCATION (IF OTHER THAN BETHESDA)
5. NCI-227 — SERIAL NO.

6. Purine Precursors in E. coli — PROJECT TITLE

7. Paul T. Condit — PRINCIPAL INVESTIGATOR(S)

8. — OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: The goal of this project is to identify the various compounds which serve as purine precursors for E. coli.

Methods Employed: The sulfanomide - inhibited system of Shive (J. Biol. Chem., 172:69) is used, in which the accumulation of the purine precursor 4-amino-5-imidazolecarboxamide serves as an index of the efficacy of a compound as a purine precursor.

Major Findings: The following compounds have been tested and found to be inactive as precursors in this system: glycinamide, N-formylglycine, aminomalonic acid, hydantoic acid, hydantoin, aminomalonamide, formylaminomalonamide, ureidomalonamide and formylaminomalonamamidine. Improved syntheses have been developed for aminomalonic acid and ureidomalonamide.

Significance to Cancer Research: The pathways of the biosynthesis of purines are of interest to the general problem of cancer chemotherapy for several reasons. After the individual compounds have been identified, structural analogues can be prepared which may behave as metabolic antagonists. It is possible that such antagonists may be useful chemotherapeutic agents. A comparison of biosynthetic pathways in normal tissues and in tumors may lead to the discovery of other exploitable metabolic differences.

Proposed Course of Project: The synthesis and testing of other potential precursors will continue during the coming year. In particular, glycinamide ribotide, which has been shown to be a precursor of inosinic acid in pigeon liver in vitro, will be investigated in this bacterial system.

PROJECT REPORT FORM (Cont'd)

10. NCI - 227
SERIAL NO.

11.
BUDGET ACTIVITY:

RESEARCH	[X]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	TECHNICAL ASSISTANCE	[ ]

12.
COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 or 1957.

13.
IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

No entries for items 14, 15 and 16.

PROJECT REPORT FORM

1. N.C.I. (INSTITUTE) 2. OADR (LABORATORY OR BRANCH)

3. Clinical Pharmacology & Experimental Therapeutics (SECTION OR SERVICE) 4. (LOCATION (IF OTHER THAN BETHESDA)) 5. NCI-228(C) (SERIAL NO.)

6. Tissue Culture of Human Neoplasms
PROJECT TITLE

7. William C Mohler
PRINCIPAL INVESTIGATOR(S)

8.
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: 1) To develop practicable and reliable techniques of growing neoplastic cells from human biopsy material in order to
a) provide new human cell lines for cancer research,
b) serve as the basis for developing a "clinical" test for the sensitivity of a patient's tumor to one or more therapeutic compounds.

Methods employed: Several different tissue culture techniques are being evaluated. Biopsy material is being planted in "T-flasks", Roller Tubes, and embryologic watch glasses. Plasma clots are being avoided if possible. Explants are placed directly on glass substrate or on glass beneath perforated cellophane. Eagle's "semi-defined" medium is being compared to "undefined" media similar to those used by Earle, Chang, Enders, and Zitcer.

Patient material: Biopsy material is obtained from therapeutic or diagnostic operations on patients admitted to other programs in the N.C.I.

Major findings: 1) Ten (10) biopsies have been followed for at least 2 weeks.
a) Five (5) of these have grown out cell lines which have been successfully transferred and appear to be established.
b) Two (2) are still growing but are not ready for transfer.
c) Two (2) "grew" abortively but then died.
d) One (1) was contaminated and was discarded before growth could be estimated.

PROJECT REPORT FORM (cont'd)

2) Of the established cell lines it is impossible to say whether these are neoplastic or normal cells, or mixtures. Leighton's "sponge techniques" will be employed to help identify their nature.

Significance to Cancer Research: Cancer research and chemotherapy have been limited by the lack of ways to isolate and maintain human neoplasms outside of their original hosts. This project hopes to find ways of culturing neoplastic cells from a high percentage of biopsies. If pure strains of cells are established, they may well be of use elsewhere in the N.C.I. or N.I.H.

It seems likely that in the near future no compound will be successful in the chemotherapy of all types of cancer. An assay method employing patient biopsies may prove of value in choosing treatment when several drugs are being considered. If a correlation is found between in vitro and in vivo drug effect, it will lend more credence to the results of tissue culture as a screening method for new cancer drugs.

Proposed course of project: 1) Further investigation of the effect of different media, substrates and methods of handling tissue to obtain neoplastic cell growth from a higher percentage of biopsies.

2) Preliminary work on "dose-time-effect" curves for several compounds including HN_2 and Thio TEPA on established cell lines.

3) Trial of compounds on replicate cultures of patient biopsy material.

PROJECT REPORT FORM (cont'd)

NCI-228(C)
SERIAL NO.

BUDGET ACTIVITY:

RESEARCH	/X/	ADMINISTRATION	/__/
REVIEW & APPROVAL	/__/	TECHNICAL ASSISTANCE	/__/

COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 or 1957

IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

1. Nutritional requirements of normal and neoplastic cells - H. Eagle, NMI
2. Growth of normal and neoplastic cells in sponge matrix - J Leighton, NCI
3. Projected screening of potential chemotherapeutic compounds on established lines of "normal" and "malignant" cells under aegis of the Screening Panel of the Cancer Chemotherapy National Committee.

NO ENTRIES FOR ITEMS 14 15 and 16.

PROJECT REPORT FORM

1. N.C.I. (INSTITUTE) 2. OADR (LABORATORY OR BRANCH)

3. Clinical Pharmacology and Experimental Therapeutics (SECTION OR SERVICE) 4. (LOCATION (IF OTHER THAN BETHESDA)) NCI-229(C 5. Was 700(C (SERIAL NO.)

6. Pharmacology of Riboflavin Analogues
PROJECT TITLE

7. Montague Lane
PRINCIPAL INVESTIGATOR(S)

8. C O. Brindley
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: The objective of this project is to determine. in human patients with neoplastic diseases the pharmacology of a series of riboflavin analogues which are effective in treating animal tumors.

Methods employed: Photofluorometric techniques are employed to measure flavin levels in plasma and urine prior to and following drug administration. Chromatography is used to determine the metabolic products of the drugs Bio-assays are utilized to study the biological activity of these products.

Patient material: Ten patients with neoplastic disease participated in the pharmacological studies with U-2112 and one patient is currently under study with U-6538

Major findings: The major findings in the study of one such compound 6,7 - dimethyl - 9 - (2' -acetoxyethyl) isoalloxazine. or U-2112, are that the compound is poorly absorbed and that it is almost completely converted by man into three other flavins.

Significance to Cancer Research: These drugs have been shown to inhibit the growth of rat tumors by antagonizing riboflavin. These studies are designed to obtain information in regard to desirable dosage for man. methods of drug administration, and signs of drug toxicity. The absorption, distribution and metabolic fate of these drugs are of importance in evaluating their clinical effects. Data derived from a few patients may make possible prediction of the activity of members of this class of compounds. If riboflavin deficiency can be produced it will be possible to test the effects of such deficiency upon neoplasms in man.

PROJECT REPORT FORM (CONT'D)

Proposed Course of Project: Attempts will be made to isolate the metabolic products of these drugs from man and from rats and test them individually in bacterial systems for activity as riboflavin antagonists. Clinical pharmacology studies with sodium -6,7 dimethyl -9 - isoalloxazine succinate, or U-6538, will be continued to establish human dosage and obtain information in regard to drug efficacy and toxicity. Plasma and urine levels, drug distribution and metabolic fate will also be studied.

PROJECT REPORT FORM (cont'd)

Was (700 (C))
1. ~~NCI 229(C)~~
SERIAL NO.

1.

BUDGET ACTIVITY:

RESEARCH	[X]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	TECHNICAL ASSISTANCE	[ ]

2.

COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 OR 1957.

3.

IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

NO ENTRIES FOR ITEMS 14, 15 & 16.

PROJECT REPORT

1. National Cancer Institute — Institute
2. Lab. of Chemical Pharmacology — Laboratory or Branch
3. Office of the Chief: — Section or service
4. _____ — Location (if other than Bethesda)
5. NCI-250 — Serial No.
6. Report of the Chief: Planning and Coordination of Investigations, Organized in an Interdisciplinary Team Approach, on Basic Science Aspects of Cancer Chemotherapy. — Project Title
7. Murray J. Shear — Principal Investigator(s)
8. _____ — Other Investigators

9. PROJECT DESCRIPTION

A. General

This has been a year of transition and re-organization. With the appointment of a Clinical Director interested in cancer chemotherapy as a primary objective, the stage was set for formulation of a "complete" program of research in chemotherapy at the N. C. I. At the request of the Associate Director in Charge of Research, the Chief of this Laboratory together with the Clinical Director, drew up plans for an N. C. I. chemotherapy program and submitted them in June. These plans call for activities in all the facets of this subject, viz., selection of new agents, acquisition, screening, pharmacology in animals, experimental therapeutics, clinical pharmacology and evaluation for therapeutic effectiveness in cancer patients.

The role of this Laboratory in the N. C. I. program was delineated as one of research in the basic science aspects of cancer chemotherapy, and of close cooperation with the other parts of the N. C. I. engaged in this field. The staff of this Laboratory made contributions to the clinical program, apart from planning on overall and specific matters, by participating in numerous group conferences with their clinical colleagues, by giving consultation from their experience in animal tumor chemotherapy, and by active participation in several of the projects of the clinical investigators. Three people, with a background of several years work in this Laboratory, were transferred to Clinical Pharmacology.

Project Report(cont'd)

This past year saw other major developments in the organization of a enlarged national program in cancer chemotherapy, in which the Laboratory Chief participated by invitation. A U.S. Cancer Chemotherapy National Committee was brought into being. The Cancer Chemotherapy National Service Center was established in Bethesda as the operating arm of this Committee. he Chief of the Biochemistry Section of this Laboratory was transferred to the Center for service as full-time Consultant in Screening.

My current relation to these new groups is that of Liaison Member fr the International Union Against Cancer, in my capacity as Chairman of the U on Chemotherapy Committee. The latter Committee, upon the request of the Int rnational Research Commission of the Union, has scheduled two Regional Sym osia on Cancer Chemotherapy Research: a European Symposium will be held Oslo, Norway, during the week of May 20, 1956; a Pacific Region Symposium will be held in Tokyo, Japan, in June of 1957.

B. Specific

The technical reports on the various projects in the research progr m of this Laboratory are given in the accompanying statements of the major in vestigators on the staff.

Future Course

Increased attention will be given during the year ahead to macromolecules such as polysaccharides and lignosulfonates; and to the mechanisms of their biological effects, including their destructive action on tumors. Duri the recent past we have opened a new field by extending our findings with bacterial polysaccharides to analogous, and chemically different, polymeric materials which we have isolated from higher plants, from normal organs and from tumor

Among the techniques we propose to use, in addition to those mentioned in the accompanying reports, are some borrowed from immunology and immunochemistry. For this line of research, we have recruited a leading investigator in the field of polysaccharide immunology.

Reorganization

Towards the close of 1955, final approval was given to the reorganization of the structure of this Laboratory and to the reassignment of personnel as justified. The Office of the Chief is now an administrative unit, and the researches are conducted in four groups designated as follows:

Project Report (cont'd)

Organic Chemistry Section
Polysaccharide Section
Cellular Pharmacology Section
Biochemical Pharmacology Section

Dr. Haruo Sato, after working here for three years as a visiting scientist, returned in November to Japan to assume the headship of a new unit in Experimental Pathology. Arrangements are being made for another young colleague of Prof. Yoshida to come here, for research in cytochemistry, for a year or two. Dr. Daphne Papadopoulou, Head of the Biochemistry Dept. at the Cancer Institute in Athens, Greece, who is in this country as a Fellow of the Amer. Assn. of University Women, came as a Guest Worker to this Laboratory.

NO ENTRIES FOR ITEMS 10, 11, 12, 13, 14, 15, and 16.

PROJECT REPORT

1. National Cancer Institute — INSTITUTE
2. Laboratory of Chemical Pharmacology — LABORATORY OR BRANCH
3. Organic Chemistry — SECTION OR SERVICE
4. — LOCATION (IF OTHER THAN BETHESDA)
5. NCI 251 — SERIAL NO

6. Isolation, synthesis, and determination of structure of chemical agents useful in damaging animal or human tumors, or in studying the pharmacologic action of such drugs. — PROJECT TITLE

7. J. L. Hartwell — PRINCIPAL INVESTIGATOR(S)

8. A. Schrecker, D. Vivian, R. B. Ross, J. Wood, A. Goldin, M. Belkin, J. Leiter, D. Fitzgerald, A. Perrault, and M. J. Shear — OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Project: Isolation, synthesis, and determination of structure of chemical agents useful in damaging animal or human tumors, or in studying the pharmacologic action of such drugs.

Objectives: To develop chemical agents which are useful in influencing animal or human tumors, or in studying the mechanism of action of such drugs.

Methods employed: Chemical compounds are either isolated from plants or animal tissues, or are synthesized. Methods of isolation and purification depend entirely on the particular tissue used, and include solvent extraction, chromatography, ion exchange resins, paper electrophoresis, and countercurrent extraction. Methods of synthesis run the gamut of organic chemistry, depending on the type of compound desired. When compounds of unknown structure are isolated, the most recent methods of organic chemistry are used to elucidate their structure, including degradative and synthetic chemical reactions, and ultraviolet and infrared spectroscopy. Fate and distribution of several labelled tumor-necrotizing drugs can now be studied in animals, with tracer atom techniques. For the identification of metabolic products of these drugs, techniques have been worked out involving paper chromatography and paper electrophoresis.

PROJECT REPORT (Cont'd)

Major findings: 1. Stereochemistry of Lignans. The configuration of podophyllotoxin and its relation to most of the other lignans was reported last year. Present work has as its aim the determination of absolute configuration of the lignans, thus relating them to the other great classes of natural products: amino acids, sugars, and steroids. The lignan chosen, on which work is progressing, is guaiaretic acid.

2. Physico-chemical Studies on Podophyllotoxin. The polymorphism and isomorphism of this compound have been studied. The project has been completed.

3. Synthesis of Possible Biochemical Intermediates. Work has been begun on the synthesis of possible biochemical intermediates in the metabolism of nicotinamide antagonists.

4. Synthesis of Improved Vital Stains. This work, centering on the structure of Neutral Red, has been continued from last year. The three structures most likely to represent the commercial stain Neutral Red were synthesized, and only one found to possess staining properties. However, it was unexpectedly found that this compound exists in three different modifications, only one of which stained. A method has been found of converting certain other non-staining phenazine derivatives into staining modifications. The chemistry of these modifications is being worked out.

Two more monohalogenated phenazines, the 1-bromo and 1-iodo derivatives, have been synthesized, thus making available all the monohalogenated phenazines except the 1-fluoro derivative.

5. Chemistry of Polysaccharides of Bacterial, Plant and Animal Tissue. The work reported last year has been extended to the identification of the constituent sugars of a number of natural polysaccharides.

Infrared studies on a number of plant polysaccharides have enabled a pronounced band at 8.7-8.8 microns to be ascribed to the presence of the α-anomer.

Two materials of animal origin, both highly active in producing tumor-damage, were found to be composed largely of nucleic acid.

A number of methods were tried in an attempt to purify polysaccharide fractions without destroying tumor-damaging activity.

6. Isolation and Identification of the Tumor-Damaging Agent of Alangium villosum Bark. Work has progressed on the fractionation of the alkaloids. These alkaloids appear to be a complex mixture of compounds, some of which are active and some inactive in producing damage in tumors. The most efficient methods for their separation are being studied.

PROJECT REPORT (Cont'd)

7. Isolation and Identification of the Tumor-Damaging Agents in Bryonia. Work has been resumed on the fractionation of the root of this plant. It is an extremely complex product. Beside the active polysaccharide reported last year, sterol, glucosidic, and other fractions have been obtained which are being studied.

8. Preparation for Determining Fate and Distribution of C^{14} - tagged Colchicine in Mice. A paper-chromatographic method was worked out for the separation of colchicine and its impurities. Using this method, it has been determined that the sample of colchicine prepared 3 years ago with C^{14} in ring A is still of good quality. This proved that during this time the tagged colchicine had not undergone decomposition from its own beta-ray bombardment. This conclusion was confirmed by radioautograph experiments. In the course of this work, the extreme sensitivity of colchicine to even short exposures of U.V. light was discovered; this has an important bearing on analytical techniques for the detection of colchicine and its derivatives.

Several more dry-run syntheses of trimethyl colchicinic acid methyl ether d-tartrate have been carried out, and the yield improved.

Considerable time was spent checking the new Tracerlab counting equipment, especially the Superscaler and Automatic Flow Gas Counter. Both were found to have dangerously high electrical "shorts", and the latter had a tendency to go into continuous discharge. It is believed that the first of these difficulties has been reduced to a safe condition, and the second has beeneliminated. Preliminary sample thickness correction curves for radioactivity measurement of $BaCO_3$ have been prepared for each of two Flow Counters.

9. Isolation and Identification of Tumor-Damaging Agents from Bulbs of the Family Amaryllidaceae. See Report of Biochemistry Section. This work has now been transferred to the Organic Chemistry Section.

10. Isolation and Identification of Tumor-Damaging Agents from Conifers. See Report of Biochemistry Section. This work has now been transferred to the Organic Chemistry Section.

11. Lignosulfonates and Other Wood Products. A constituent of sulfite waste liquor from the processing of conifer wood into paper, active in damaging tumors, has been isolated and identified as calcium lignosulfonate. This substance is very soluble in water and is relatively non-toxic to animals. Work has been directed toward determining the effect of different variables on the activity. The variables include: species of tree from which the waste liquor is derived, the pulping process used on the wood, degree of sulfonation, degree of polymerization, and nature of metal combined with the sulfonic acid.

Other active agents have been isolated from the wood and bark of certain trees and the poducts are being studied chemically.

PROJECT REPORT (Cont'd)

10 NCI 251
SERIAL NO.

11 BUDGET ACTIVITY:

RESEARCH	/X/	ADMINISTRATION	/_/
REVIEW & APPROVAL	/_/	TECHNICAL ASSISTANCE	/_/

NO ENTRIES FOR ITEMS 12 & 13

14 NCI 251
SERIAL NO.

15 PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1955:

1. Schrecker and Hartwell, "Application of Tosylate Reduction and Molecular Rotations to the Stereochemistry of Lignans", J. Am. Chem. Soc. 77, 432 (1955).

2. Schrecker, Hartwell, Maury and Leiter, "Components of Podophyllin. XVII. Ionic Derivatives of Podophyllotoxin and of the Peltatins". Scheduled for J. Am. Chem. Soc. 77, Dec. 1955.

3. Schrecker, Hartwell and Alford, "Components of Podophyllin. XVIII. Polymorphic Modifications of Podophyllotoxin. Provisionally accepted by J. Org. Chem.

4. Vivian, Hartwell and Waterman, "Phenazine Syntheses. IV. Nitriles". J. Org. Chem. 20, 797 (1955).

5. Leiter, Perrault, Hartwell, Kline and Shear, "Negative Results with Diphenylethylamines in Producing Damage in Sarcoma 37". Cancer Research, Suppl. No. 2, 109 (1955).

NO ENTRIES FOR ITEM 16

PROJECT REPORT

1. National Cancer Institute — INSTITUTE
2. Laboratory of Chemical Pharmacology — LABORATORY OR BRANCH
3. Cellular Pharmacology — SECTION OR SERVICE
4. _____ — LOCATION (IF OTHER THAN BETHESDA)
NCI-5.252 — Ser.No.

6. Pharmacologic Action of Tumor Damaging Substances on Animal and Human Malignant Cells. — PROJECT TITLE

7. Morris Belkin — PRINCIPAL INVESTIGATOR(S)

8. H. Sato, E. Essner, R. B. Ross, D. L. Vivian, J. Leighton, D. Lavie, A. Perrault, I. Kline, I. Wodinsky — OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objective

Development of novel drugs, primarily from plant sources; and to study these and a variety of other tumor-necrotizing compounds to determine how they bring about cell damage and cell death.

Methods

Techniques of pharmacology, histo- and cytochemistry and tissue culture are used. New techniques are developed as necessary.

Major Findings

For each of the several phases of this research program, the principal findings are as follows:

I. Tumor Damaging Capacity of Plant Materials. The testing of more than 100 Australian plants for tumor-necrotizing capacity against Sarcoma 37, and other tumors, has been completed and the results are being prepared for publication.

PROJECT REPORT (Cont'd)

Four of these plants caused consistent tumor damage. Fractionation of the bark of Alangium villosum has to date yielded two fractions (1) an alkaloid, isolated in crystalline form with a melting point of 255°, which is inactive against Sarcoma 37 and (2) a lower melting fraction 161-163°, presumably an alkaloid, which actively damages Sarcoma 37 and has a favorable range between the minimum effective dose and the toxic dose.

Further fractionation for the active principles of Bryonia alba and dioica (wild bryony root) has yielded extracts whose components have been separated into neutral, acidic and basic fractions. The steral content was found to be high.

In collaboration with Dr. David Lavie of the Weizmann Institute in Israel, who supplied them, testing of fractions of Ecballium elaterium (squirting cucumber) for tumor damaging activity was begun. A number of fractions have to date exhibited potency in this respect.

II. Studies in Cellular Pharmacology.

a) 20 plant polysaccharides were each given I.P. in one dose to CAF_1 mice carrying S37 ascites tumor. Most of these substances had previously been shown to damage intramuscular implants of S37.

Of this number, polysaccharides from S. marcescens and Bryonia alba and dioica caused direct cellular damage consisting of marked cytoplasmic vacualization and cellular swelling. Nuclei were relatively unaffected. (A MS. embodying these findings has been submitted to the J. of Biophysical and Biochemical Cytology.)

b) Two of 16 induced mouse hepatomas were successfully converted to the ascitic form. The ability to form ascites tumors appeared to be related to intrinsic growth speed and not to degree of anaplasia. Survival time of both ascites hepatomas and a derived subline decreased with serial transplantation. (These findings are being readied for publication.)

c) The effect of Nitromin (Nitrogen mustard-N-oxide) on cells of Sarcoma 37 ascites and a hepatoma ascites was investigated. The principal cellular effects of this drug were (1) a decrease in mitotic rate (2) an increase in mitotic abnormalities (3) a pronounced increase in cell volume. Both types of cells responded in essentially similar fashion. (These data are now being readied for publication.)

PROJECT REPORT (CONT'D)

III. Synthesis of Improved Vital Stains.

This past year, most emphasis has been placed on new methods of synthesis of neutral red and closely related compounds with the aim of extending our knowledge of this and other vital stains. Some unexpected results have been obtained, showing that neutral red exists in no less than three forms, only one of which stains living cells. These as yet not completely explained phenomena lead to a number of applications of practical value in vital staining.

The chemical aspects of this project are described in Dr. Vivian's report, from the Organic Chemistry Section.

IV. Response of Human Malignant Cells to Drugs, and the Effect of Drugs on the Invasive Properties of Such Cells in Tissue Culture.

a) The destructive invasion of normal human tissues (liver, adrenal, bone, lung and brain) by human malignant cells has been further studied. The human tumors were strain HeLa (Gey) (from an epidermoid carcinoma of the cervix); strain KB (Eagle) (from a carcinoma of the mouth); strain J-96 (Osgood) (from a monocytic leukemia). Each tumor invaded the normal tissues.

b) Tissue cultures of strain HeLa were exposed to varying concentrations of Acetylpodophyllotoxin-ω-pyridinium chloride (N.C.I. #3022). Six hours of exposure to even the minimum concentration of 0.0001 mg/ml produced metaphase arrest and chromatin fragmentation in all dividing cells.

Proposed Course of Project

Most phases of this project will be continued. Continued stress will be placed on obtaining information concerning the mechanisms by which necrotizing compounds produce cellular damage; and to correlate, at the cellular level, between the pharmacologic action of drugs and the functional and structural responses in relation to treatment. Such information is urgently needed in the effort to develop newer and better drugs for the use of investigators working in clinical chemotherapy of cancer.

PROGRESS REPORT (Cont'd)

10. NCI 252
SERIAL NO.

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11. BUDGET ACTIVITY:

RESEARCH	[x]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	TECHNICAL ASSISTANCE	[ ]

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12. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 or 1957:

Collaborating with Dr. David Lavie of the Weizmann Institute, Rehoboth, Israel, on the fractionation and bio-assay of Ecballium elaterium for the active principles responsible for its tumor-damaging ability.

NO ENTRIES FOR ITEMS 13, 14, 15 & 16

PROJECT REPORT

1. National Cancer Institute — 2. Laboratory of Chemical Pharmacology
INSTITUTE — LABORATORY OR BRANCH

3. Biochemical Pharmacology — 4. — 5. NCI 253
SECTION OR SERVICE — LOCATION (IF OTHER THAN BETHESDA) — Serial No.

6. Biochemical and Pharmacological Studies of Host-Tumor Relationship in Tumor Chemotherapy
PROJECT TITLE

7. Dr. A. Goldin
PRINCIPAL INVESTIGATORS

Dr. L. Shuster, S. Humphreys, J. Venditti, P. Condit, Prof. N. C. Kaplan, B. I. Burton
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Project: Biochemical and pharmacological studies of host-tumor relationship in tumor chemotherapy.

Objectives: 1. Study of metabolic transformations and the mechanism of action of metabolic antagonists with respect to tumor and host.
2. Establishment and employment of new therapeutic principles and procedures in the management of tumor growth in animals.

Methods employed: Macrobiological assay procedures involving methods of inhibition analysis for animals with and without tumors. In vivo and in vitro biochemical procedures.

Major findings: 1. Host-tumor relationships. Growth studies were undertaken on the host-tumor relationship with Sarcoma 37 in mice to serve as a basis for subsequent chemotherapeutic studies. A general similarity was observed between the results with S37 in mice with thoseof Mider et al who employed the Walker carcinoma 256 in rats, suggesting similarity of underlying mechanisms. The similarities are as follows: (a) Despite the reduction in food intake for cancerous animals, after the onset of progressive tumor growth these animals continued to gain in total weight at a rate

comparable to (or faster) than their non-cancerous controls, (b) in contrast to the continued growth in total weight of cancerous animals, control animals on a diet isocaloric to them were unable to maintain their weight, the decline in weight coinciding with the onset of progressive tumor growth for the cancerous animals; (c) initially, the carcass (animal minus tumo of the cancerous animal increased in weight, but began to decline as the tumor became manifest. The tumor itself continued to grow at a rapid rate, eventually attaining, in some cases, a size comparable to that of the carcass of the cancerous animal.

Older mice survived longer and the tumor attained heavier weights, as contrasted with younger mice. This also occurred when the tumor inoculum was reduced.

2. Influence of the host. The antileukemic action of aminop- terin was demonstrated to be influenced by the age of the mouse. Aminopterin was more effective in increasing the survival time of older mice with leukemia as compared with younger mice. This increase was attributable to two factors (a) without treatmen older leukemic mice survive longer than younger leukemic mice following inoculation of an equal number of leukemic cells. At least part of the effect of age on the survival time is attributable to the initial weight of the mouse. The percentage "take" of the leukemia is not influenced by the age of the mouse. (b) Older mic tolerate a higher dose of aminopterin, but this increased toleranc is not transmitted to the tumor. This permits the employment of higher doses of aminopterin in older mice with a resultant increase in antileukemic action.

3. Influence of number of leukemic cells. Leukemic mice were kept alive for an extended period of time with massive dose of amethopterin. The leukemic cells from such mice showed on transplant little if any evidence of resistance. Apparently other factors, such as a diminution in the tolerance of the host to treatment, or progressive increase in the number of leukemic cells, despite treatment, may render a treatment ineffective.

This suggested an investigation of the influence of the numbe of cells in the leukemic inoculum on the effectiveness of treatme An approximately linear relationship was observed between the number of cells in the leukemic inoculum necessary to kill 50% of the mice, and the dosage of amethopterin. Thus, the effective ness of treatment is influenced by the number of leukemic cells in the host.

4. Treatment of advanced leukemia. Advanced leukemia in mice is susceptible to therapy if an appropriate modification of treatment schedule with amethopterin is applied. In contrast to heavier and less frequent treatment with amethopterin when the tumor is in its earlier stages, the optimal schedule of treatment when therapy is initiated late, is one in which very light doses of amethopterin are administered rather frequently. The levels of therapy which were effective against advanced tumor were so low as to produce relatively little early toxicity. The food intake and

PROJECT REPORT (Cont'd)

weight of mice so treated were maintained at high levels for a substantial period.

5. Pyridine nucleotide synthesis in the mouse (with Dr. N.O. Kaplan, McCollum Pratt Inst., Johns Hopkins). A tenfold increase in the concentration of liver diphosphopyridine nucleotide (DPN) was observed in liver following the injection of nicotinamide in mice. Maximum biosynthesis occurred in 8-12 hours. An elevation of DPN also occurred in spleen, kidney, and neoplastic tissue. 6-mercaptopurine inhibited the rise as well as the subsequent breakdown of DPN. This was partially reversed by administration of adenylic acid. Injection of DPN and deamino DPN also increased the DPN content of liver and kidney. Nicotinic acid and tryptophane also promoted an increase in liver DPN, but the magnitude of synthesis was much smaller than with nicotinamide. Uniformly C^{14}- labeled and C_1 labeled glucose are incorporated to approximately equal extent in biosynthesized DPN (Shuster). In both cases the specific activity of the nicotinamide mononucleotide moiety of the DPN was approximately twice that of the adenylic acid.

6. Drug action (with Dr. Robert Burton, Lab. of Neurochemistry N.I.N.D.B.). Serotonin appeared considerably less effective than Marsilid in potentiating nembutal anesthesia. Marsilid increases the side position time induced by the non-barbiturate, Doriden. Reserpine appears to potentiate amphetamine stimulation. Preliminary studies show that reserpine gives some extension of survival time with leukemia in mice.

7. Study of transformations involving citrovorum factor (CF) (with Dr. Paul Condit, General Medicine Branch). Administration of folic acid (FA) one hour prior to aminopterin afforded optimal protection. Direct determination of total CF in mouse liver showed a maximum concentration one hour after administration of FA. These observations are being extended to changes which occur following administration of antifolics.

Significance of Cancer Research: (Name of Institute) These experiments are designed to provide basic information pertaining to the host-tumor relationship in chemotherapy. From such studies, principles may be established for treatment in animals which may be of use in application to clinical chemotherapy.

Proposed course of project: During the next year the various phases of this work will be continued and broadened.

PROJECT REPORT (Cont'd)

10. NCI 253
SERIAL NO.

11. BUDGET ACTIVITY:

RESEARCH	[x]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	TECHNICAL ASSISTANCE	[ ]

12. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 or 1957.

Collaboration with Dr. N. O. Kaplan of the McCollum-Prat Institute, Johns Hopkins University.

Funds, facilities and staff have been provided by Dr. Kaplan in joint program.

NO ENTRIES FOR ITEM 13

PROJECT REPORT (Cont'd)

4. NCI 253
ERIAL NO.

5.
UBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING
ALENDAR YEAR 1955.

1 Factors influencing the specificity of action of an antileukemic agent
(minopterin). Multiple treatment schedules plus delayed administration
c citrovorum factor. A. Goldin, J. M. Venditti, S. R. Humphreys, D. Dennis,
I. Mantel, and S. W. Greenhouse. Cancer Research 15: 57-61, 1955.

2 Potentiation of pentobarbital anesthesia by isonicotinic acid hydrazide
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N. Mantel. In press, Cancer Research.

. Growth studies on Sarcoma 37 in mice. A. Goldin, S. R. Humphreys,
. M. Venditti, D. Dennis and N. Mantel. In press, J. Nat. Cancer Inst.

16.
HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT
DURING CALENDAR YEAR 1955.

A. Goldin received reappointment as Research Associate in the McCollum-Pratt Institute of the Johns Hopkins University, Balt., July 1955.

PROJECT REPORT

1. National Cancer Institute
INSTITUTE

2. Laboratory of Chemical Pharmacology
LABORATORY OR BRANCH

3. ORGANIC CHEMISTRY
SECTION OR SERVICE

4. _____
LOCATION (IF OTHER THAN BETHESDA)

5. NCI 256
SERIAL NO.

Preparation of Supplement to Hartwell's "Survey of Compounds Which Have Been Tested for Carcinogenic Activity"
PROJECT TITLE

J. L. Hartwell
PRINCIPAL INVESTIGATOR(S)

Prof. P. Shubik, The Chicago Medical School
OTHER INVESTIGATORS

PROJECT DESCRIPTION

Project: Preparation of Supplement to Hartwell's "Survey of Compounds Which Have Been Tested for Carcinogenic Activity"

Objectives: To prepare a supplement to my "Survey", similar in format, covering the literature on chemical carcinogenesis from 1948 to 1954.

Methods employed: This is a literature survey. All the original literature from all the countries in the world, is culled for pertinent references which are then abstracted. The abstract journals are also scanned for further references. All material abstracted is typed on cards. From these cards a final manuscript copy is typed. Numerous indexes will be prepared. Printing will probably be by varitype.

Major Findings: No conclusions can be drawn from this compilation until it is completed and all the data tabulated.

significance to CANCER Research: (Name of Institute) This continued project, as a literature survey of chemical carcinogenesis, is expected to be useful to research workers here, and in the rest of the world, in the same way that the original "Survey" has been. It is being kept up to date at the request of the National Research Council transmitted through the Surgeon General.

PROJECT REPORT (Cont'd)

Proposed Course of Project: This particular Supplement should be completed within the coming calendar year. It is likely that periodic supplements will be prepared from time to time in the future, depending on the rate of progress in this field in this and in other countries.

PROJECT REPORT (Cont'd)

10. NCI 256
SERIAL NO.

11. BUDGET ACTIVITY:

RESEARCH	/x/	ADMINISTRATION	/_/
REVIEW & APPROVAL	/_/	TECHNICAL ASSISTANCE	/_/

12. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 or 1957:

Prof. P. Shubik is cooperating in this project under a Professional Service Contract.

NO ENTRIES FOR ITEMS 13, 14, 15 & 16

PROJECT REPORT

1. ational Cancer Institute — 2. Lab. Chemical Pharmacology
Institute — Laboratory or Branch

3. Biochemistry — 4. — 5. NCI-257
Section or Service — Location(if other than Bethesda) — Serial No.

6. Chemical and Pharmacological Studies with Tumor-Necrotizing Polysaccha-
Project Title (rides and with Chemically-defined Substances known
(to Damage Animal Tumors.

7. Margaret G. Kelly and J. Leiter
Principal Investigator(s)

8. Norman Smith, Sue Roethel, I. Wodinsky and David P. Rall
Other Investigators

9. PROJECT DESCRIPTION:

Objectives:

Determination of (1) chemical composition of tumor-necrotizing polysaccharides, and isolation, and identification of active and inactive components. 2) Pharmacological actions of tumor-necrotizing polysaccharides, especially hoe actions which help elucidate mechanisms involved in production of tumor-ierorrhage and necrosis. (3) Collaborative studies with surgical staff on compounds isolated from podophyllin. (4) Correlation of structure of phenazine analogues and derivatives with tumor-affecting potency and with toxicity.

Methods employed:

Biochemical, biological, pharmacological, histochemical and bacteriological methods, modified as required to fit specific problems of the research.

Major findings:

(1) The soluble and insoluble polysaccharide materials isolated by Adian Perrault from Bryonia root were hydrolyzed with sulfuric acid and paper-chromatographed. Both fractions appear to have the same constituents: a

reducing dissacharide (either cellobiose or maltose) and glucose. No pentoses, sugar acids, ketoses, amino acids, or phosphate esters were found. An unidentified substance, migrating at the approximate rate of glucosamine, but which did not give the Morgan and Elson reaction for hexosamines, was also present.

It had been found previously that the polysaccharide from Serratia marcescens could be incorporated into a synthetic media as the sole source of carbohydrate for the following micro-organisms: A. fumigatus; A. oryzae; A. niger; and a mutant fungus isolated from a polysaccharide preparation in this laboratory. Attempts have been made to isolate enzymes from these organisms which would break down the polysaccharide materials into oligosaccharide intermediates in order to obtain information on the simplest configuration which would retain tumor-damaging potency. It has been established that the cell bodies and cell-free filtrates contain enzymes which slowly break down the polysaccharide to reducing sugars. After 96 hours incubation with preparations from ultra sonerated cell bodies and hydrolyzed cell-free filtrates, about 10% of the polysaccharide was hydrolyzed to reducing sugar, without detectible loss of tumor-damaging activity. No intermediates have been demonstrated with paper chromatography.

(2) Studies designed to elucidate the Shwartzman phenomenon in rabbits were undertaken in collaboration with Dr. David Rall. For details, see report of Rall.

Although attempts to elicit a Shwartzman reaction in mice have not been successful in the past, this problem was reinvestigated. If this could be done, a direct correlation would be possible between the Shwartzman reaction and tumor-hemorrhage in the same animal by use of drugs known to inhibit the Shwartzman in rabbits. It seemed possible that, with the greater variety of inbred strains of mice which are available today, a strain of mouse might be found which was Shwartzman active. Negative results were obtained with 10 strains of mice. However, two strains showed 40-50% incidence of skin hemorrhage and necrosis after the intradermal injection of polysaccharide; and 1 strain (C57 Bl.) gave a high incidence (80-90%) of local hemorrhagic response after the intradermal injection. The response could be observed grossly and microscopically in 24 hrs., and was somewhat more pronounced in 48 hrs. As no enhancement of response, or no increase in number of positive responses could be obtained after the intravenous (or "provocative") dose of polysaccharide, this does not represent the classis Shwartzman reaction. However, preliminary results indicate that, just like the Shwartzman reaction in rabbits, this local hemorrhage response in mice following the intradermal injection of polysaccharide can be inhibited by sympatholytic and anti-coagulant drugs. When the sympatholytic drug, chlorpromazine, was given to mice bearing 6 day implants of S-, a two to three times larger dose of polysaccharide was required for production of tumor damage. On the other hand, when tumor-bearing mice were treated with anti-coagulants, there was little if any change in dose response (tumor-hemorrhage) to polysaccharide.

Experiments are in progress to determine the lactic acid content of skin from prepared and normal sites of rabbits and mice, and to study in vitro their aerobic and anaerobic glycolysis. Thomas and Stetson have reported a higher lactic acid content, and an increased rate of glycolysis of skins "prepared" with bacterial toxins and polysaccharides, and our results to date corroborate this.

The development of tolerance to bacterial polysaccharide has often made impractical the effective use of many of its pharmacologic actions. Recently, Farr et al and others reported that incubation at 37° C. of bacterial pyrogens with plasma, or serum, enhanced fever response, particularly in tolerant rabbits. We were unable to substantiate these observations. (For details, see Rall's report)

We have investigated the effect of incubation with serum on tumor response and lethality in tolerant and non-tolerant (fresh) mice. Tolerance was developed by two i.p. injections of polysaccharide in saline (4 mg. per mouse) given 4 days apart; tumors were implanted one day later. This schedule induced tolerance both to toxicity (20-fold increase in LD_{50}) and to tumor-damaging potency (70-fold increase in ED_{50}) of the polysaccharide. ED_{50} and LD_{50} of polysaccharide incubated at 37° C. in fresh rabbit serum or in saline (controls) were determined in CAF_1 mice on the 6th day of tumor growth.

Incubation with serum for 1/2 hour did not significantly change ED_{50} or LD_{50} of polysaccharide in tolerant or non-tolerant mice. Incubation for one hour at 37° C. however, significantly increased the LD_{50}. Toxicity was decreased about 30% in tolerant, and 60% in fresh mice. ED_{50} was not significantly changed. The ratio of LD_{50} to ED_{50} increased from 2.6 to 3.6 in the tolerant group, and from 6.8 to 18.6 in the fresh animals. The active agent in rabbit serum appears to be heat-labile; preheating the serum to 70° C. for 10 minutes before incubation with polysaccharide at 37° C. for 1 hr. prevented the increase in LD_{50}.

(3) Further collaborative studies were made with the surgical staff in three patients. The drugs used were alpha-peltatin, and acetylpodophyllotoxin- ω -pyridinium chloride. In one patient with recurrent epidermoid carcinoma, it was possible to get preliminary information on: route of administration--topical compared with intratumoral; effect of solubility--alpha-peltatin is relatively insoluble in water, acetylpodophyllotoxin- ω -pyridinium chloride is soluble (both drugs are members of the podophyllin group, and have comparable effects when given systemically to mice with S-37 implants); optimum concentration--dose ranges from 5% to 20% were studied by topical route, and from 1 mg. to 150 mg. by intratumoral route; and vehicle--phosphate buffer, dextran, propylene glycol, and lanolin were tried. Treated and untreated areas were biopsied and studied in the pathology laboratory (Dr. Louis Thomas). An effort was made to ascertain depth of penetration, severity of tumor damage, and onset and duration of

drug effect. (Maximum tolerated dose and toxic symptoms of acetylpodophyllo toxin- ω -pyridinium chloride were determined in dogs.)

In connection with the anticipated clinical studies, a comparison of effec by intratumoral and intraperitoneal routes of administration was made with mouse Sarcoma 37. Alpha-peltatin and acetylpodophyllotoxin- ω -pyridinium chloride were used in this investigation. In giving the drugs i.t., the dose wa divided, and several injections were made around the circumference of the tumor and at the base. With both routes, and with both drugs, areas of appar ently unaffected, viable tumor tissue could be found microscopically, particu- larly at the periphery and adjacent to large blood vessels. No clear-cut gross or microscopic evidence was obtained which would indicate any advantage to be obtained by i.t. route, even when the total amount of an effective i.p. dose was injected directly into the tumor tissue.

(4) The tentative relationship between structural configuration and trem rs which was suggested from earlier investigations, is still apparent from addi- tional compounds which have been added to the series. Two piperazines did n produce tremors, but the 3 pyrazinium compounds which were tested did produce tremors. There does not appear to be any correlation between tumor damage and toxicity (tremors); the only correlation between structure and tumor- damaging action is that of quaternization.

Significance to Cancer Research

(1) Tumor-necrotizing polysaccharides are complex substances. An information concerning the features of structure which are essential for their tumor-necrotizing action would be important. Preparation--or synthesis--of more effective and less toxic analogues could then be attempted with a greater degree of rationality.

(2) Any information on the mechanism of action involved in productio of hemorrhage and necrosis in animal tumors is of fundamental as well as pra- tical interest. It should help in the development of a rational approach to can cer chemotherapy, and aid in the more effective use of the materials now at hand.

(3) These studies served to orient clinicians on the effects and limita tions of these compounds, and to furnish data on which to base any future clini cal studies with these compounds.

(4) This rather extensive series of chemically related, tumor-damag ing compounds offered a splendid opportunity for trying to correlate structure with pharmacologic action, with the expectation that such information would serve as a better guide for future synthesis of related compounds with more desirable properties.

Proposed Course of Project

(1) Study of the action of aqueous and alcoholic extracts of ultrasonerate fungi on polysaccharide materials, and attempt to isolate and characterize intermediate products. It is proposed to use some crude polysaccharide preparations, also, in the hope that they will be more susceptible to attack than the more highly purified, and possibly altered, materials investigated to date. As the treatment does not seem to alter the tumor-necrotizing action of the polysaccharides, even though increasing the reducing sugars, an attempt will be made to characterize these altered products by obtaining ultra-violet spectra, total carbohydrate content, reducing sugars and hexosamine levels.

(2) The studies on mechanism of action of the Shwartzman phenomenon in rabbits are virtually completed, and no further work is proposed other than preparing the data for publication. (See report of Rall)

The nature of the hemorrhagic response elicited in certain strains of mice on intradermal injection of Shwartzman-active polysaccharides will be studied further. The possibility that this may be related to the Arthus phenomenon is being considered. Work is in progress to determine whether variation of the time interval between the intravenous and intradermal injections may yield a true Shwartzman reaction in mice. It is also planned to study the effect of tolerance on production of the Shwartzman phenomenon. The effect of anticoagulants, of autonomic blocking agents, and of leucopenic drugs on production of tumor-hemorrhage and on the local skin hemorrhage in mice will continue to be studied.

Lactic acid metabolism of skin injected with Shwartzman-positive and Shwartzman-negative polysaccharides will continue to be studied. The effect of drugs known to inhibit the Shwartzman reaction will be examined in parallel experiments with fresh and tolerant rabbits and mice. The lactic acid metabolism of skins of mice, from strains which give a hemorrhagic response to an intradermal injection, and from those which give no gross or microscopic evidence of any response, will be studied.

The results to date of the effect of incubation of polysaccharide with serum have been submitted as an abstract for presentation at the 47th meeting of American Cancer Society and are also being prepared in manuscript form for publication. It is planned to continue these investigations in an attempt to identify the active agent in serum and to determine whether incubation with serum will influence the development of tolerance to polysaccharide.

10. NCI-257

Serial No.

11.

Budget Activity:

Research	/x/	Administration	/_/
Review and approval	/_/	Technical assistance	/_/

NC ENTRIES FOR ITEMS 12 and 13

14. NCI-257

15.

Publications other than abstracts from this project during calendar year 1955

Rall, David P., Smith, Norman H., and Kelly, Margaret G.: Effect of Anticoagulants on Local Shwartzman Reaction. Proc. Soc. Exp. Biol. Med. 88: 241-243, 1955.

NO ENTRIES FOR ITEM 16

PROJECT REPORT

1. National Cancer Institute
INSTITUTE

2. Laboratory of Chemical Pharmacology
LABORATORY OR BRANCH

3. Biochemistry
SECTION OR SERVICE

4.
LOCATION (IF OTHER THAN BETHESDA)

5. NCI 258
SERIAL NO.

6 Enzyme Changes Induced in Normal and Malignant Tissues with Chemical Agents.
PROJECT TITLE

7 V. S. Waravdekar and J. Leiter
PRINCIPAL INVESTIGATOR(S)

8 O. H. Powers and L. D. Saslaw
OTHER INVESTIGATORS

9 PROJECT DESCRIPTION

A. Objectives

To elucidate the mechanism of action of tumor-damaging agents by determining the biochemical changes produced in tumors as contrasted with normal tissues.

B. Methods Employed

1) Mice, with and without tumors, are injected with tumor-damaging agents (acetylpodophyllotoxin-ω-pyridinium chloride, α-peltatin, colchicine derivatives, etc.). Animals are sacrificed at frequent time intervals (before and after gross damage in tumors is observable) and the biochemical properties determined. A broad spectrum of enzymes were determined: glycolytic, oxidative, purine metabolizing enzymes; dehydrogenases involved in protein metabolism; etc.

2) The effects on subcellular components were also evaluated using different techniques of disruption (sonic-vibrations, passing through a tissue press, etc.).

C. Major Findings

1) Experiments on glucose utilization (reported last year) showed a decreased ability of tumors from treated animals to use glucose unless the medium were fortified with a large excess of diphosphopyridine nucleotide (DPN). These observations were extended to an evaluation of the role of DPN in the metabolism of normal and malignant tissues from drug-treated mice. Endogenous DPN (also reported last year) was markedly reduced in tumor tissue following an injection of these tumor-damaging agents. Investigation revealed that relatively little change occurred in the DPNase activity (including DPN-pyrophosphatase). Even after 24 hours, when marked damage was observable, the DPNase activity of treated tumors was virtually the same as that from untreated. The ability to synthesize DPN (synthesizing enzyme) on the other hand was markedly affected. Only 50 percent of the activity was observed 4 hours after injection as compared with tumors from control, uninjected mice.

2) It was observed that the liver of animals bearing Sarcoma 37 had a reduced DPN synthesizing activity over that observed in livers from non-tumor-bearing animals. The values decreased steadily for four or five days following tumor implantation and leveled off at a value of about one half of the activity of livers from non-tumor-bearing mice (0.475 μM. DPN synthesized/mg.N/hr.).

3) Following injection of acetylpodophyllotoxin-ω-pyridinium chloride, the DPN synthesis of liver from treated tumor-bearing mice increased, while the activity in the tumor (see item 1) decreased markedly. Liver activity rose to 130 percent of controls while tumor activity dropped to about 40 percent of controls.

4) It had been previously reported that succinoxidase activit was markedly diminished following drug injection, but the dehydrogenase activity was found virtually unaffected; the relation of this phenomenon to the Slater effect was examined. The other two electron transfer systems, malic oxidase and isocitric oxidase [which act through coenzyme I and II (DPN and TPN)]were also examined. Both oxidases were markedly reduced, whereas the dehydrogenase activities were scarcely affected. Other enzyme systems closely related to these (viz. malic-cytochrome c reductase, DPN-cytochrome c reductase, $DPNH_2$ oxidase and TPN-cytochrome c reductase) were all reduced in a fashion parallel to the oxidases.

5) Preliminary experiments revealed no specific relationship between the above changes (item 4) and the Slater factor. The effects of BAL (specific) and of drugs were distinguished by determining succinoxidase activity in the presence and absence of

ytochrome c and after treatment with calcium phosphase gel. he effects seem to be accounted for primarily by the effects on he cytochrome system.

6) Glutamic dehydrogenase, DPNase and DPN-pyrophosphatase ctivities (hitherto unreported) were determined for a group of umors (Sarcomas 37 and 180; Carcinomas C3HBA, 2h1-6, and 63; lymphoma 1, 2 and MOL; Leukemia L1210; Harding-Passey melanoma; nd Hepatoma 129).

7) The effect of a variety of the particulate and soluble, on-sedimentable enzymes [DPN synthesizing enzyme (nucleus); ricase, glutamic dehydrogenase (mitochondria); adenosine deaminase nd nucleoside phosphorylase (supernatant)] were examined to valuate the role of morphologic changes to the chemical ones. he changes observed were not related to any particulate structure, or were they related to the changes produced by physical dis- uption of particulates (such as cytochrome oxidase, etc.). DPN ynthesizing activity was decreased more markedly by drug treat- ent than by physical disruption; glutamic dehydrogenase activity as somewhat decreased by treatment but very greatly increased by onoration; uricase was markedly decreased following drug treat- ent but unchanged by disruption of mitochondria.

D. Significance to Cancer Research

1) This project has developed data which describe the damage nduced in tumors by chemical agents in biochemical terms as well s morphologic ones. This may lead to a better understanding of rug action on tumors and to a better selection of agents, or com- inations of agents, for cancer therapy.

2) The observations on the effects of drugs on glucose utili- ation are complemented and fortified by those of Drs. Woods and Burk who have been investigating the relationship of these and other tumor-damaging agents on glycolysis, particularly in rela- ionship to hormonal influences (a stress-modifiable insulin and anti-insulin factor). Cooperative relationship with these inves- igators has been maintained.

3) The observations on reduced synthesis of DPN in tumor- bearing mice needs considerable extension, before its full sig- nificance can be assessed. It appears superficially related to either or both the observations made some time ago by Greenstein and his collaborators on liver catalase, and currently and inde- pendently by Shacter on the role of liver sulfhydryl. Unlike catalase, however, DPN synthesizing enzyme was found in measurable quantities in both tumor and liver, and the changes in enzyme in

both types of tissue could be followed. The response of liver sulfhydryl to tumor growth seems to be a less delicate index, since changes are not observable for several days after tumor implantation.

E. Proposed Course of Project

Further work, including extension to other tumors and tissues, will clarify these points and the other findings reported in Section C.

PROJECT REPORT (Cont'd)

10. NCI 258
SERIAL NO.

11. BUDGET ACTIVITY:

RESEARCH	[x]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	TECHNICAL ASSISTANCE	[ ]

NO ENTRIES FOR ITEMS 12 and 13

PROJECT REPORT (Cont'd)

14. NCI 258
SERIAL NO.

15. PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1955:

1) Enzyme changes induced in normal and malignant tissues with chemical agents. IV. Effect of Alpha-peltatin on glucose utilization by Sarcoma 37 and on the adenosine triphosphotase, Hexokinase, Aldolase and Pyridine nucleotide levels of Sarcoma 37. V. S. Waravdekar, A. D. Paradis and J. Leiter: J. Nat. Cancer Inst. 16, 31-39, 1955.

2) Enzyme changes induced in normal and malignant tissues with chemical agents. V. Effect of acetylpodophyllotoxin-ω-pyridinium chloride on uricase, adenosine deaminase, nucleoside phosphorylase and glutamic dehydrogenase activities. V. S. Waravdekar, A. D. Paradis and J. Leiter: J. Nat. Cancer Inst. 16, 99-105, 1955.

NO ENTRIES FOR ITEM 16

PROJECT REPORT

1. National Cancer Institute — Institute
2. Lab. of Chemical Pharmacology — Laboratory or Branch
3. Biochemistry — Section or Service
4. — Location(if other than Bethesda)
5. NCI-259 — Serial No

6. Fractionation of Plants, and Bioassays for Tumor-Necrotizing Potency — Project Title

7. D. B. Fitzgerald, J. Leiter, J. L. Hartwell — Principal Investigator(s)

8. A. Schrecker — Other Investigators

9 PROJECT DESCRIPTION

A) Objective

Isolation, from plant sources, of drugs with ability to induce damage in Srcoma 37. Bioassays of chemical compounds for the presence of this biologi-cl property.

B) Methods

Individual chemical compounds, or extracts of plant tissues, are inject-e into mice bearing 6 day old implants of Sarcoma 37; the animals are sacrificed 2 hours later and observed for damage induced in the tumors. Crude plant ex-tacts are fractionated by solvent partition and/or by chromatographic techniques ad assayed for tumor-damaging potency.

C) Major findings

1. Bulbs from the family Amaryllidaceae were selected because of their ctivity as antimalarials and because of the findings that some groups of com-pounds (e.g. Daraprin) had potency both as antimalarials and as anti-tumor agent. bout 75 species from 25 genera of Amaryllidaceae were tested; 45 species be-nged to the genus Narcissus. In general, there was a close correlation be-veen tumor-damaging potency and taxonomic classification. Even within the

10 NCI-259
Serial No.

11

Budget Activity:

Research /x/ Administration /__/

Review and approval /__/ Technical assistance /__/

NO ENTRIES FOR ITEMS 12, 13, 14, 15 and 16.

PROJECT REPORT

1 National Cancer Institute — 2. Laboratory of Chemical Pharmacolog
INSTITUTE — LABORATORY OR BRANCH

3 Office of the Chief — 4. _____ — 5. NCI 26.(
SECTION OR SERVICE — LOCATION (IF OTHER THAN BETHESDA — Serial No

6 Pharmacologic Actions of Bacterial Polysaccharides.
PROJECT TITLE

7 David P. Rall
PRINCIPAL INVESTIGATOR(S)

8 N. H. Smith, Margaret G. Kelly and James R. Gaskins
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objective

To elucidate the mechanism of action of polysaccharide with particular emphasis on its activity in the local Shwartzman reaction and on its pyrogenic action.

Methods

Pharmacological and histological methods were employed.

Major Findings

We have demonstrated that Biscoumacetate (Tromexan) inhibits the local Shwartzman reaction, as had been previously reported for heparin, indicating that anticoagulation per se is inhibitory. For the first time, peripheral vasoconstriction has been shown to be important in the pathogenesis of the Shwartzman phenomenon. This has been demonstrated by blocking the reaction with autonomic blocking drugs and by provoking the reaction, in the absence of the customary intravenous injection of polysaccharide, with small amounts of locally injected vasoconstrictors.

PROJECT REPORT (Cont'd)

The Shwartzman reaction does not occur in mice. We have demonstrated that an histologically similar reaction occurs in certain strains of mice following an intradermal injection of polysaccharide. The subsequent intravenous polysaccharide injection does not influence this reaction, thus this is not the classic Shwartzman reaction.

Incubation of polysaccharide with serum has been reported to augment its pyrogenic action in normal and tolerant rabbits We have demonstrated that such augmentation does not occur in the Shwartzman reaction or in the mouse reaction, and that, under certain circumstances, the pyrogenic activity of serum-polysaccharide is diminished.

Significance to Cancer Research

This bacterial polysaccharide has activity in producing damage in tumors; information on the mechanism of any of actions is potentially useful in making it a more effective agent.

Proposed Course

These studies are virtually completed and future efforts will be in the nature of tying up loose ends and writing up the remaining material for publication.

PROJECT REPORT (Cont'd)

0. NCI 260
SERIAL NO.

1. BUDGET ACTIVITY:

RESEARCH	[x]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	TECHNICAL ASSISTANCE	[ ]

NO ENTRIES FOR ITEMS 12 and 13

PROJECT REPORTS (Cont'd)

14. NCI 260
SERIAL NO.

15. PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1955:

Effect of Anticoagulants on Local Shwartzman Reaction. Rall, David P., Smith, Norman H. and Kelly, Margaret G.: Proc. Soc. Exp. Biol. Med. 88, 241-243, 1955.

NO ENTRIES FOR ITEM 16

PROJECT REPORT FORM

1. NCI (INSTITUTE) 2. Laboratory of Biochemistry (LABORATORY OR BRANCH)

3. Protein Chemistry (SECTION OR SERVICE) 4. -------- (LOCATION (IF OTHER THAN BETHESDA)) 5. NCI-300 (SERIAL NO)

6. Polycysteine Peptides and Proteins
PROJECT TITLE

7. Greenstein, Winitz, and Wade (Visiting Scientist)
PRINCIPAL INVESTIGATOR(S)

8. ----------
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

The objectives of this project have been given in last year's report. The major findings of the past year are as follows.

The oxidation of L-cysteinyl-L-cysteine has been investigated by aeration in aqueous solution over the pH range 4.5-10.7 and at concentrations of 0.015-3.0%. Paper chromatographic analysis indicated that a mixture of at least 3 ninhydrin-reactive components resulted. The proportion of low R_f (in phenol) (0.00-0.15) high molecular weight material was found to be lower in the products of oxidation carried out at the more dilute levels. The proportion of the other two components varied with the pH of the solution during oxidation. Outside the pH range 7.0-9.6 the formation of high R_f (0.49) component was favored almost to the exclusion of the medium R_f (0.18) component. The latter, however, was formed in appreciable quantities within this pH range. Molecular weight determinations by a new ultracentrifuge technique developed by Kegeles on the pure high R_f (0.49) component showed this to be the cyclic monopeptide to which the designation "cyclo-L-cystinyl" has been given. Similar determinations on mixtures of the R_f 0.18 and 0.49 components indicated that the R_f 0.18 component is very probably dimeric. Application of the dinitrophenyl technique to the study of these compounds demonstrated that this dimeric component consists largely of "parallel" cystinylcystine, but the possibility of the presence, in addition, of the "antiparallel" isomer cannot be excluded.

10. NCI-300
SERIAL NO.

11.
BUDGET ACTIVITY:

RESEARCH	[x]	ADMINISTRATION	[ ]
REVIEW AND APPROVAL	[ ]	TECHNICAL ASSISTANCE	[ ]

NO ENTRIES FOR ITEMS 12, 13, AND 14.

15.
PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1955

1. M. C. Otey and J. P. Greenstein, Studies on Polycysteine Peptides and Proteins. II. Apparent Dissociation Constants, and Ultraviolet and Infrared Absorption Spectra of Isomeric Cystinylcystine Peptides. Archiv. Biochem. and Biophys., 53 501 (1954).

2. R. Wade, M. Winitz, and J. P. Greenstein, Studies on Polycysteine Peptides and Proteins. III. Configurations of the Peptides of L-Cystine Obtained by Oxidation of L-Cysteinyl-L-Cysteine. J. Am. Chem. Soc., in press.

16.
HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1955.

None

PROJECT REPORT FORM

1. NCI
INSTITUTE

2. Laboratory of Biochemistry
LABORATORY OF BRANCH

3. Office of the Chief
SECTION OR SERVICE

4. ---------
LOCATION (IF OTHER THAN BETHESDA)

5. NCI-301
SERIAL NO

6. Secretarial Duties in the Laboratory of Biochemistry
PROJECT TITLE

7. B. A. Mitchell, C. Cissel, A. Sigwald (M. Fisher), and V. Patkus
PRINCIPAL INVESTIGATOR(S)

8. ---------
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

The objectives of the Secretarial Unit in the Office of the Chief are to: Maintain personnel, correspondence, reprints, and requisition files, keep an accurate and current record of Laboratory library, type manuscripts, letters, memoranda, lantern slides, requisitions, shop orders, and miscellaneous articles and charts. The above duties are performed for 40 professional employees and for 28 subprofessional employees.

Since January 1955, this Unit has typed the following: Approx. 2800 original pages of manuscripts, approx. 1456 letters and memoranda, approx. 90 lantern slides, approx. 775 pages of miscellaneous material, approx. 2055 requisitions, approx. 125 Cancer Instrument shop orders, approx. 225 NIH Instrument Section orders, approx. 200 maintenance work requests, approx. 185 requests for services, approx. 70 reports of surplus property, approx. 60 shipment requests, and approx. 85 requests for animals.

PROJECT REPORT FORM (Cont'd)

10. NCI-301
SERIAL NO.

11.
BUDGET ACTIVITY:

RESEARCH	[x]	ADMINISTRATION	[ ]
REVIEW AND APPROVAL	[ ]	TECHNICAL ASSISTANCE	[ ]

NO ENTRIES FOR ITEMS 12, 13, 14, 15, AND 16.

PROJECT REPORT FORM

1. NI
INSTITUTE

2. Laboratory of Biochemistry
LABORATORY OR BRANCH

3. Office of the Chief
SECTION OR SERVICE

4. --------
LOCATION (IF OTHER THAN BETHESDA)

5. NCI-302
SERIAL NO

6. Spectrophotometric and Micro-Ultramicroanalysis
PROJECT TITLE

7. I. J. Koegel, R. A. McCallum, J. F. Williams, and G. E. McNeill
PRINCIPAL INVESTIGATOR(S)

8. -------
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

The service function of the Analytical Unit remains essentially as described in previous annual reports. The efficiency continues to remain at a high level as indicated by the following facts:

(a) The senior member has devoted 90.0% of his time to the infrared and ultraviolet spectrophotometric program.

(b) During 1955, 1,900 samples were submitted for analysis making a total of some 5,800 individual tests performed. These figures represent a 33.0% increase in the work load compared with 1954, and as there has been no increase in staff the efficiency of the unit is apparent.

The infrared and ultraviolet spectrophotometric program continues as outlined in the 1954 report.

Objective: The spectrophotometric program of this unit remains as outlined in the 1954 report, with the additional object of developing quantitative techniques for estimating end groups in di, tri, and tetrapeptides.

Methods Employed: The spectrophotometric program remains essentially as outlined in the 1954 annual report, however during 1956 emphasis will be placed upon the use of heavy water (D_2O) techniques.

Major Findings: The solid state infrared spectra of approximately 93 dipeptides have been studied and the absorption peaks which reflect the following vibrational motions of the unit structures identified:

(a) ν (-N-H), ν (C=O), and δ(N-H) of the peptide bond.

(b) The asymmetrical and symmetrical deformation motions of the hydrogen atoms of the methyl and methylene units of structure.

(c) The asymmetrical and symmetrical stretching motions of the end group carboxylate ion.

(d) The symmetrical stretching, ν (N-H) and deformation motions δ(N-H) of the a-amino end group of the dipeptide.

Utilizing the shifts in the wavelengths of the above identified absorbtion peaks as the structural units were altered about the peptide bond, it was possible to demonstrate that the resonating polar form of the peptide link does make a significant contribution to the total peptide structure. Pauling has previously made this observation however there have been statements in the current literature questioning whether the resonating polar form of the peptide bond makes any contribution to total peptide structure.

It was demonstrated that structural units such as methyl, methylene and C-H groups in complex molecules such as amino acid, di, tri, and tetrapeptides absorb in the infrared at approximately the same wavelengths as in the simple straight chained paraffins.

Significance to Cancer Research: Essentially as described in previous reports; however, the preciseness with which the absorbtion peaks of the infrared spectra may be correlated with specific structural units suggests that these functional groups may be quantitatively estimated in di, tri, and tetrapeptides. Quantitative procedures of this type would greatly expedite identification and estimation of such compounds.

Proposed Course of Research: To continue the infrared and ultraviolet spectrophotometric program as outlined in the previous annual report with emphasis on the quantitative estimation of the end groups specifically (NH_3^+) and ($C\overset{O}{\underset{O}{}}$) in di, tri, and tetrapeptides.

10. NCI-302
SERIAL NO.

11.
BUDGET ACTIVITY:

RESEARCH	[x]	ADMINISTRATION	[ ]
REVIEW AND APPROVAL	[ ]	TECHNICAL ASSISTANCE	[ ]

NO ENTRIES FOR ITEMS 12, 13, AND 14.

15.
PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1955

1. R. J. Koegel, J. P. Greenstein, S. M. Birnbaum, M. Winitz, and R. A. McCallum, Studies on Diastereoisomeric α-Amino Acids and Corresponding α-Hydroxy Acids. V. Infra-red Spectra. J. Am. Chem. Soc., 77, 5708 (1955).

16.
HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1955.

None

PROJECT REPORT FORM

1. NCI — INSTITUTE
2. Laboratory of Biochemistry — LABORATORY OR BRANCH
3. Protein Chemistry — SECTION OR SERVICE
4. ---------- — LOCATION (IF OTHER THAN BETHESDA)
5. NCI-304 — SERIAL NO

Studies on L and D Amino Derivatives of Carcinogenic Amines
PROJECT TITLE

Greenstein, Winitz, and Birnbaum
PRINCIPAL INVESTIGATOR(S)

Brooks, Whitaker
OTHER INVESTIGATORS

PROJECT DESCRIPTION

The objectives of this project have been given in last year's report. The major findings of the past year are as follows:

The carbobenzoxy derivatives of the following L and D amino acids have been synthesized: alanine, butyrine, norvaline, norleucine, S-benzylcysteine, methionine, valine, leucine, isoleucine, phenylalanine, tryptophan, in addition to glycine and L-proline. These have been combined through the mixed anhydride procedure through their carboxyl groups with the amino groups of 2-aminofluorene, 4-aminobiphenyl, and 4,4'-diaminobiphenyl, crystallized and characterized, and subsequently subjected to HBr in glacial acetic acid to remove the carbobenzoxy group. The free compounds were purified and subjected to hydrolytic studies with homogenates of rat liver, kidney, spleen, lung, intestine, and pancreas. Compounds containing L-amino acids with straight aliphatic side-chains were the most susceptible to hydrolysis, those with aromatic groups or with branching on the side-chains were much less susceptible, while those compounds containing D-amino acids, with a few weak exceptions, were completely inert.

The compounds were combined into pellets with purified cholesterol and inserted subcutaneously into rats. It is still too early to tell what the effects are.

PROJECT REPORT FORM (Cont'd)

10. NCI-304
SERIAL NO.

11.
BUDGET ACTIVITY:

RESEARCH	[x]	ADMINISTRATION	[ ]
REVIEW AND APPROVAL	[ ]	TECHNICAL ASSISTANCE	[ ]

NO ENTRIES FOR ITEMS 12, 13, AND 14.

15.
PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1955

1. J. P. Greenstein, M. Winitz, and S. M. Birnbaum, Studies on Carcinogenic Amines. I. L- and D-Amino Acid Derivatives of 2-Aminofluorene, 4-Aminobiphenyl, and 4,4'-Diaminobiphenyl, and their Susceptibility to Hydrolysis by Tissue Homogenate J. Am. Chem. Soc., 77, 5721 (1955).

16.
HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1955.

None

PROJECT REPORT FORM

1. NCI — INSTITUTE
2. Laboratory of Biochemistry — LABORATORY OR BRANCH
3. Protein Chemistry — SECTION OR SERVICE
4. ---------- — LOCATION (IF OTHER THAN BETHESDA)
5. NCI-306 — SERIAL NO
6. The Large Scale Resolution of Amino Acids — PROJECT TITLE
7. Winitz, Marshall (Visiting Scientist), Birnbaum, Greenstein — PRINCIPAL INVESTIGATOR(S)
8. -------- — OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

To further perfect the techniques for preparing large quantities of optically pure amino acids.

Methods: Large scale resolutions are routinely in progress in the laboratory. Close observation of these procedures and modifications of the techniques employed are continuously under way. The methods employed, of course, vary with the problem that is presented. In general they include the preparation of new racemic derivatives, new enzymes or the introduction of different methods of incubation.

Major findings: 1) For the preparation of the L isomers alone, initial substrate concentrations up to 1 molar have proven satisfactory. 2) Observation of the ease of direct crystallization of acetyl-D-arginine from the concentrated resolution mixture allows the procurement of better, more consistent yields of the extremely rare and expensive isomer D arginine. This isomer has never before been available in quantities suitable for nutritional, pharmacological or metabolic studies.

Significance to Cancer Research: The improvement of resolution techniques allows the production of greater amounts of optically pure amino acids for metabolic and nutritional studies on the nature of cancerous growth. It is also devoutly hoped that continued emphasis on the availability and optical purity of the amino acid isomers will stimulate commercial and research organizations into the production and employment of better defined biochemical materials.

Proposed course of research: Problems will for the most part be considered as they appear. In addition the resolution of such previously unresolved amino acids as α-aminopimelic, β-hydroxyglutamic acid, 3-4-dihydroxy-phenylalanine, 3-5 diiodo tyrosine, benzylpenicillamine and others will be investigated.

10. NCI 306

SERIAL NO.

11.

BUDGET ACTIVITY:

RESEARCH	[x]	ADMINISTRATION	[ ]
REVIEW AND APPROVAL	[ ]	TECHNICAL ASSISTANCE	[ ]

NO ENTRIES FOR ITEMS 12, 13, AND 14.

15.

PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 19

1. S. M. Birnbaum, M. Winitz, and J. P. Greenstein, A Simplified Preparation of D-Arginine. Arch. Biochem. and Biophys., In Press.

16.

HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1955.

None

PROJECT REPORT FORM

1. NCI (INSTITUTE) 2. Laboratory of Biochemistry (LABORATORY OR BRANCH)

3. Protein Chemistry (SECTION OR SERVICE) 4. ---------- (LOCATION (IF OTHER THAN BETHESDA)) 5. NCI-307 (SERIAL NO)

6. Studies on Diastereoisomeric α-Amino Acids and Corresponding α-Hydroxy Acids
PROJECT TITLE

7. M. Winitz, J. P. Greenstein, S. M. Birnbaum and R. J. Koegel
PRINCIPAL INVESTIGATOR(S)

8. N. Izumiya, L. Bloch-Frankenthal, C. G. Baker, M. C. Otey,
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: To ascertain the effect of the configuration of secondary asymmetric centers in α-amino- and α-hydroxy acids on chemical, physical and biological systems.

Methods Employed: The methods utilized included optical rotation and optical rotatory dispersion which involved the use of a photoelectric polarimeter, infra-red spectra, and enzymatic methods wherein the Warburg manometric and van Slyke apparatus were employed. Enzymes were prepared and fractionated according to standard procedures.

Major Findings:

Configuration of β-Asymmetric center of Isoleucine

By virtue of the greater susceptibility of L-acyl-L-amino acids over D-acyl-L-amino acids to the action of renal acylase I, a method of determining the optical configuration of the β-asymmetric center of isoleucine has been developed. For this purpose, dl-α-methylbutyryl-L-norleucine was subjected to the action of the enzyme, yielding as a hydrolytic product a mixture of free (+) and (-) α methylbutyric acids in which the former predominated. Since (+) α-methylbutyric acid is derivable from L-isoleucine (and D-alloisoleucine), the β-asymmetric center of these stereomers has been assigned the L-configuration. On the basis of the known configuration of the β-asymmetric centers of the isomeric isoleucines, threonines and phenylserines, a correlation between the configuration of this center and the extent of susceptibility of the α-asymmetric center to various L- and D- directed enzyme systems has been noted.

Rotatory Dispension of Diasymmetric Amino Acids

The optical rotatory dispersion of 42 L-amino acids was studied at 589, 578, 546, 435, 405 and 365 mμ. and described for the most part in terms of a two constant Drude equation. The empirical relation

between the rotatory characteristics of the α-amino acids and the magnitude of proposed by Patterson and Brode was tested in this large series of compounds and, in modified form, was found to be generally applicable to amino acids with a single α-asymmetric center as well as to the α-asymmetric center of diastereoisomeric amino acids.

Infrared Spectra:

The infrared absorption spectra in the solid state have been observed for fifty-three pairs of optically enantiomorphic α-amino acids, including five diasymmetric amino acids, in the wave-length range 2μ to 15μ. No differences were noted in the spectra of the corresponding L- and D-forms of these compounds, but differences in varying degrees were noted between the diastereoisomeric forms of each of the amino acids with two centers of optical asymmetry. Most of the amino acids possessed a remarkable similarity in the 6.3μ to 7.5μ region of the spectrum, with a somewhat lesser uniformity in the 3.3μ, 3.9μ, and 4.7μ regions. Using the spectra of the group of homologous straight-chain α-amino acids as a prototype, it was possible in some cases to follow the effect of substituents on this chain by progressive shift in absorption bands in the 6μ region.

Rotatory Dispersion of Copper Complexes:

The optical rotatory dispersion of the copper complexes of six diasymmetric L-amino acids, as well as their L-allo-stereomers, was studied at 578, 546, 435, 405, and 365 mμ. Calculations of the contribution (partial molar rotation) of the α- and ω-asymmetric centers to the observed molar rotation were effected and the empirical relation between the rotatory characteristics of the copper complexes of α-amino acids and wave length proposed by Pfeiffer and Henseleit tested. It was found that this relation, while inapplicable to the total molar rotation of diastereomeric amino acids, nonetheless becomes entirely applicable when based upon the partial rotation of the α-center of asymmetry.

Effect of β-Configuration on Enzymic Action:

A correlation between the β-configuration of α,β-diasymmetric amino acids and the susceptibility exhibited by these compounds to ten different ophio L-amino acid oxidases and two different D-amino acids oxidases has been noted. An α-D-β-D-configuration (for D-amino acid oxidases) and an α-L-β-L-configuration (for L-amino acid oxidases) led to a more marked enzymic susceptibility than their corresponding diastereomers. The four optical antipodes of threonine and isoleucine served as substrates in the aforementioned. Extension of such relationship to the four stereoisomers of O-methylthreonine, as well as those of γ-hydroxy-β-methylvaleric acid, has been effected.

The racemic O-methylthreonine, as its acetyl and chloroacetyl derivatives, and O-methylallothreonine, as its formyl derivative, were resolved by a general enzymic resolution procedure developed in this Laboratory whereas nitrous acid deamination of the four

No. 9 cont'd. NCI-307

optically pure isomeric isoleucines provided the corresponding α-hydroxy-β-methylvaleric acids. Oxidation rates of the former four enantiomorphs were determined with D- and L-amino acid oxidases, as were the hydrolytic rates for the formyl, acetyl and chloroacetyl derivatives with renal acylase I. Correspondingly, L-hydroxy acid oxidase (rat kidney) gave oxidation rates for the stereoisomeric L-α-hydroxy-β-methylvaleric acids, as well as eleven other L-α-hydroxy acids. The corresponding D-α-hydroxy acids were prepared for comparison purposes.

In addition, the susceptibility, to hog kidney aminopeptidases, of several dipeptides with diasymmetric amino acid residues on the terminal amino end has been determined. The correlation of β-configuration with enzymic susceptibility was made.

Significance to Cancer Research:

The essential nature of the diasymmetric amino acids, L-isoleucine and L-threonine, as components of the diet of the rat and of the human being, draws attention to the somewhat more subtle influence of β-configuration on the behavior of the substrate in biological systems. That some enzyme systems apparently show a rather marked and characteristic response to substrates with a given β-configuration, whereas others exhibit a more random, and sometimes indifferent, response with respect to this same configuration, has been found. In this regard, biological systems appear to be endowed both with enzyme systems of seemingly capricious, as well as of directed, nature. It is perhaps through this combination of order and randomness provided by different enzymes with respect to a given configuration that the plan of nature can be effected. In any event, physical, chemical and biological studies centered on β-configurations will certainly increase our knowledge in this regard.

Proposed course of project:

A portion of the next calendar year will be devoted to an extension of the foregoing studies to other naturally occurring asymmetric systems with particular reference to their toxicity, behavior with different enzyme systems and effect on growth.

10. NCI-307
SERIAL NO.

11.

BUDGET ACTIVITY:

RESEARCH	[x]	ADMINISTRATION	[ ]
REVIEW AND APPROVAL	[ ]	TECHNICAL ASSISTANCE	[ ]

NO ENTRIES FOR ITEMS 12, 13, AND 14.

15.

PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 195

1. M. Winitz, S. M. Birnbaum and J. P. Greenstein. Studies on Diastereoisomeric α-Amino Acids and Corresponding α-Hydroxy Acids. III. Configuration of the β-Asymmetric Center of Isoleucine. J. Am. Chem. Soc., 77, 3106 (1955).

2. M. C. Otey, J. P. Greenstein, M. Winitz and S. M. Birnbaum. Studies on Diastereoisomeric α-Amino Acids and Corresponding α-Hydroxy Acids. IV. Rotatory Dispersion of the Asymmetric α- and ω-Carbon Atoms of Several Diastereoisomeric Amino Acids. J. Am. Chem. Soc., 77, 3112 (1955).

3. R. J. Koegel, J. P. Greenstein, M. Winitz, S. M. Birnbaum and R. A. McCallum, Studies on Diastereoisomeric α-Amino Acids and Corresponding α-Hydroxy Acids. V. Infrared Spectra. J. Am. Chem. Soc., 77, 5708 (1955).

4. N. Izumiya, M. Winitz, S. M. Birnbaum, and J. P. Greenstein, Studies on Diastereoisomeric α-Amino Acids and Corresponding α-Hydroxy Acids. VI. Rotatory Dispersion of Copper Complexes. J. Am. Chem. Soc., In Press.

5. M. Winitz, L. Bloch-Frankenthal, N. Izumiya, S. M. Birnbaum, C. G. Baker and J. P. Greenstein, Studies on Diastereoisomeric α-Amino Acids and Corresponding α-Hydroxy Acids. VII. Influence of β-Configuration on Enzymic Susceptibility. J. Am. Chem. Soc., In press.

16.

HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1955.

None

PROJECT REPORT FORM

1. NCI | 2. Laboratory of Biochemistry
INSTITUTE | LABORATORY OR BRANCH

3. Protein Chemistry | 4. ------- | 5. NCI-311
SECTION OR SERVICE | LOCATION (IF OTHER THAN BETHESDA) | SERIAL NO

6. Preparation and Evaluation of Various Cellulose Ion-Exchangers for the Chromatography of Macromolecules
PROJECT TITLE

7. Peterson and Sober
PRINCIPAL INVESTIGATOR(S)

8. ---------
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: To design and prepare adsorbents which permit the application of chromatographic principles to high molecular weight substances.

Methods Employed: Suitable varieties of acidic and basic groups are chemically attached to cellulose and the characteristics of the resulting cellulose ion-exchangers are evaluated with respect to adsorption and desorption of selected test macromolecules.

Major Findings: Anion- and cation-exchangers prepared from cellulose have been shown to be effective adsorbents for a variety of macromolecules, including proteins, oligopeptides*, nucleic acids*, enzymes, hormones*, etc. Sufficient experience and interest in these adsorbents has developed so that two commercial concerns are beginning to make them available.

Procedures for evaluating the adsorbents have been refined so as to provide for more rapid testing on a micro-scale.

Significance to Cancer Research: Available methods for the examination of high molecular weight components do not have sufficient resolving power to separate the multitude of macromolecular substances which are known to exist and exhibit specific biochomical

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* Indicates results obtained by other investigators with adsorbents developed in this Laboratory.

and immunochemical properties. Until suitable methods have been developed, the comparison of normal and abnormal systems must necessarily only reflect gross rather than subtle changes.

Proposed Course of Project: A variety of potential ion-exchange groups remain to be tested after incorporation into cellulose. Procedures designed to effect a more fundamental and less empirical understanding of the special nature of adsorption and desorption of macromolecules will be instituted.

PROJECT REPORT FORM (Cont'd)

10. NCI-311
SERIAL NO.

11.
BUDGET ACTIVITY:

RESEARCH	[x]	ADMINISTRATION	[ ]
REVIEW AND APPROVAL	[ ]	TECHNICAL ASSISTANCE	[ ]

NO ENTRIES FOR ITEMS 12, 13, AND 14.

15.
PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1955

1. E. A. Peterson and H. A. Sober, Chromatography of Proteins. I. Cellulose Ion-Exchange Adsorbents. J. Am. Chem. Soc., in press.

16.
HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1955

None

PROJECT REPORT FORM

1. NCI (INSTITUTE) 2. Laboratory of Biochemistry (LABORATORY OR BRANCH)

3. Protein Chemistry (SECTION OR SERVICE) 4. ---------- (LOCATION (IF OTHER THAN BETHESDA)) 5. NCI-313 (SERIAL NO)

6. Chromatographic Analysis of Protein Components of Serum in Health and Disease (PROJECT TITLE)

7. Sober and Peterson (PRINCIPAL INVESTIGATOR(S))

8. Wyckoff (OTHER INVESTIGATORS)

9. PROJECT DESCRIPTION

Objectives: To develop and apply chromatographic procedures to the resolution and isolation of the many protein components in normal and pathological serum.

Methods Employed: Serum and serum fractions are chromatographed on cellulose ion-exchangers and the effluent fractions are examined by boundary and zone electrophoresis, ultraviolet absorption, specific biological activity, dye-binding, etc.

Major Findings: Chromatographic analyses of sera have been performed and a great number of protein components have been recognized. Reproducible chromatographic patterns were obtained and practically quantitative protein nitrogen recovery was obtained. Several chromatographic components were detected in each of the globulin subdivisions. Bands of colored components could be followed down the column which corresponded to siderophilin, methemalbumin, and ceruloplasmin. Other specific components (glucosamine, orosomucoid, thrombin) were detected by chemical and immunological techniques.

A rapid short column procedure has been developed which segregates the serum proteins in groups of proteins of similar properties.

Significance to Cancer Research: A circulating fluid such as blood, which supplies nutrients and removes waste material including proteins from necrotic tissue, from all parts of the body, must reflect in some manner alterations in tissue metabolism or

composition which are the causes or consequences of disease. These new adsorbents and the chromatographic procedures, which have already demonstrated greater capacity and resolving power than other methods, provide another and more powerful approach to the understanding of the composition and function of critic macromolecular components.

Proposed Course of Project: 1. Simpler elution schedules and improved methods of characterizing the resolved components are being developed so as to conserve material and permit a more rapid examination of many samples. 2. Large scale preparation and isolation of purified fractions of clinically or biochemically desirable components will be carried out.

PROJECT REPORT FORM (Cont'd)

10. ICI-313
SERIAL NO.

11.
BUDGET ACTIVITY:

RESEARCH [x] ADMINISTRATION [ ]

REVIEW AND APPROVAL [ ] TECHNICAL ASSISTANCE [ ]

NO ENTRIES FOR ITEMS 12, 13, AND 14.

15
PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1955

1. H. A. Sober, F. J. Gutter, M. M. Wyckoff, and Peterson, Chromatography of Proteins. II. Fractionation of Serum Protein on Anion-Exchange Cellulose. J. Am. Chem. Soc., in press.

16
HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1955

None

PROJECT REPORT FORM

1. NCI
INSTITUTE

2. Laboratory of Biochemistry
LABORATORY OR BRANCH

3. Clinical Biochemical Research
SECTION OR SERVICE

4. ---------
LOCATION (IF OTHER THAN BETHESDA)

5. NCI-314
SERIAL NO

6. Metabolism of Amino and Keto Acids; Studies on Amino Group Transfer
PROJECT TITLE

7. A. Meister
PRINCIPAL INVESTIGATOR(S)

8. L. Levintow, T. Otani (Fellowship Expired Sept. 1, 1955), P. Fraser (Downey), and P. Abendschein
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: To elucidate biochemical reactions and pathways of metabolism of amino acids in normal and tumor tissues, with emphasis on mechanisms of amino group transfer and keto acid metabolism, and if possible, to relate the results of in vitro studies to investigations on intact animals and man.

Methods: Tissues are fractionated by centrifugation, salt and ethanol precipitation, and adsorption and elution techniques to yield preparations which are active in catalyzing the reactions under study. Chemical, enzymatic microbiological, and chromatographic procedures are employed in following these reactions. Substrates (metabolites or their analogues) such as amino or keto acids, peptides, etc., are prepared by synthetic organic procedures and by enzymatic methods. Isotopes such as N^{15}, C^{14}, and P^{32} are used in this work. Microbiological techniques, infrared and ultraviolet absorption studies, and polarimetry are also employed. Growth studies on rats using chemically defined diets have been carried out.

Major Findings: 1. Studies on transamination have been continued. Evidence for the participation of vitamin B6 in the glutamine-a-keto acid reaction has been obtained. Enzyme preparations obtained from isonicotinic acid hydrazide-treated rats exhibit decreased activity, which is restored by in vitro addition of pyridoxal phosphate and pyridoxamine phosphate. These studies also suggest that isonicotinic acid hydrazide treatment may be a useful tool in the study of other vitamin B6 enzymes.

2. A method for α-keto acid identification has been developed a utilized for 35 α-keto acids, including the α-keto acid analogu of most of the naturally occurring α-amino acids. By this procedure glyoxylic acid was found for the first time in human uri

3. Patients with phenylpyruvic oligophrenia have been given ora doses of glutamine or other amino acids. Glutamine administrat is followed by a marked decrease in phenylpyruvic acid and phen lactic acid excretion. No significant effect on the excretion phenylacetylglutamine was observed. Asparagine also lowers excretion of phenylpyruvic and phenyllactic acids; there is evid that asparagine administration leads to glutamine formation. T results are consistent with the concept that phenylpyruvic acid is formed in this disease by transamination; therapy involving both phenylalanine restriction and glutamine administration is suggested.

4. An investigation of the properties of the unreactive form of α-ketoglutaramic acid and related compounds has been carried ou The α-keto analogues of several ω-peptides have been prepared, including those corresponding to γ-glutamylglycine, γ-glutamyl-alanine, γ-glutamyl-β-alanine, β-aspartylglycine and β-aspartyl alanine. The product of the enzymatic oxidative deamination of L-γ-glutamyl hydrazide (pyridazinone-3-carboxylic acid) was isolated. The β-oxalacetyl-amino acids (β-oxalacetyl-glycine a β-oxalacetyl-alanine) differed from the γ-(α-ketoglutaryl)-amin acids, α-ketoglutaramic acid, and α-ketosuccinamic acid in that they were decarboxylated by hydrogen peroxide. It was conclud that the β-oxalacetyl-amino acids exist predominantly in the fr α-keto acid. Under the conditions employed, the γ-(α-keto-glutaryl)-amino acids did not participate in enzymatic transami tion. On the other hand, β-oxalacetyl-glycine and β-oxalacetyl alanine transaminated with glutamine (but not with glutamate) t form, respectively, β-aspartyl-glycine and β-aspartyl-alanine.

5. Studies on the metabolic role of α-ketoglutaramic acid have been pursued. A purified rat liver ω-amidase fraction was prepared, which hydrolyzed α-ketoglutaramic, α-ketosuccinamic, glutaramic, and succinamic acids, but did not deamidate glutamic, asparagine, and a number of other amides. The enzyme also cat lyzed the formation of succinylmonohydroxamic and glutarylmono-hydroxamic acids from the corresponding amides and relatively l concentrations of hydroxylamine; these reactions proceeded much more rapidly than did the analogous hydrolysis reactions. Both hydrolysis and transfer reactions proceeded most rapidly at abo pH 7. Preparations of guinea pig serum asparaginase and Escherichia coli glutaminase catalyzed hydroxamic acid formati from asparagine and glutamine, respectively, at rates which wo low in comparison to those of hydrolysis. In contrast to the liver ω-amidase system, high concentrations of hydroxylamine w required for hydroxamic acid formation. The pH-dependence of t reactions was determined. Succinylmonohydroxamic, β-aspartyl-hydroxamic, and γ-glutamylhydroxamic acids were hydrolyzed by

respective enzyme preparations at much slower rates than observed with the corresponding amides. In the presence of hydroxylamine, all of the enzyme preparations catalyzed hydroxamic acid synthesis from the dicarboxylic acids corresponding to the susceptible amides. This and the other findings are consistent with the concept that the transfer, hydrolysis, and synthesis reactions are catalyzed by the same enzyme. The pH-dependence of the non-enzymatic formation of hydroxamic acids from glutamine, homoglutamine, asparagine, succinamic acid, and glutaramic acid, and hydroxylamine at 37°, was studied. Non-enzymatic formation of monohydroxamic acids from aspartic, glutamic, succinic, and glutaric acids was observed at 120°. The preparation of dl-α-aminomalonamic acid, dl-β-methyl-DL-glutamic acid, dl-β-methyl-DL-glutamic acid γ-ethyl ester, and dl-β-methyl-DL-glutamine was carried out.

Significance to Cancer Research: Tumors grow and accumulate amino acid nitrogen at the expense of normal tissues of the host. It is our feeling that an understanding of the amino acid metabolism of normal and tumor tissues will be of great importance in understanding the processes involved in tumor growth. The significant function of glutamate and glutamine in amino acid and protein metabolism justify intensive investigation of the biochemical properties of these and related compounds. A truly rational system of chemotherapy of cancer may develop when these fundamental processes are elucidated.

Proposed Course of Project: Project to be discontinued at NIH, at least under supervision of present principal investigator, who plans to continue this work at Tufts University School of Medicine, Boston, Massachusetts.

10. NCI-314
SERIAL NO.

11.
BUDGET ACTIVITY:

RESEARCH [x] ADMINISTRATION [ ]

REVIEW AND APPROVAL [ ] TECHNICAL ASSISTANCE [ ]

NO ENTRIES FOR ITEMS 12, 13, AND 14.

15.
PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1955

1. A. Meister, General Reactions of Amino Acids, in Symposium on Amino Acid Metabolism. McCollum-Pratt Institute, John Hopkins University, 1955.

2. A. Meister, Transamination. Advances in Enzymology, 16, 185 (1955).

3. A. Meister, L. Levintow, R. E. Greenfield, and P. A. Abendschein. Hydrolysis and Transfer Reactions Catalyzed by ω-Amidase Preparations. J. Biol. Chem., 215, 441 (1955).

4. A. Meister, Transamination in Amino Acid Metabolism. (Symposium on Amino Acid Metabolism) Federation Proceedings, 1955.

5. A. Meister and P. Downey, Evidence for the Participation of Vitamin B6 in the Glutamine-α-Keto Acid Transamination-Deamidation Reaction. Proc. Soc. Exptl. Biol. and Med., in press, 1955.

6. A. Meister and P. A. Abendschein, Chromatography of α-Keto Acid 2,4-Dinitrophenylhydrazones and Their Hydrogenation Products. Anal. Chem., in press, 1955.

7. A. Meister, Metabolism of Glutamine. Physiol. Rev., 1955.

8. A. Meister, The Use of Snake Venom L-Amino Acid Oxidase for the Preparation of alpha-Keto Acids. International Conference on Animal Venoms, AAAS, in press, 1955.

9. A. Meister, Preparation of alpha-Keto Acids. Methods in Enzymology, vol. III, Academic Press, New York, 1955, in press

0. Patent Still Pending, "Improvements in the Manufacture of alpha-Keto Acids".

1. A. Meister, Glutaminase, Asparaginase, and ω-Amidase. Methods in Enzymology, vol. II, Academic Press, New York, 1955, in press.

16.

HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1955

Leon Levintow - Elected to membership in Society of Biological Chemists and in Association for Cancer Research.

Alton Meister - Appointed Professor and Chairman of Department of Biochemistry, Tufts University School of Medicine (July 1, 1955, on leave until January 1, 1956).

PROJECT REPORT FORM

1. NCI (INSTITUTE) 2. Laboratory of Biochemistry (LABORATORY OR BRANCH)

3. Clinical Biochemical Research (SECTION OR SERVICE) 4. ---------- (LOCATION (IF OTHER THAN BETHESDA)) 5. NCI-315 (SERIAL NO)

6. Studies on Peptides in Normal and Cancerous Subjects (PROJECT TITLE)

7. C. Baker (PRINCIPAL INVESTIGATOR(S))

8. T. Moore (Research Fellow) (OTHER INVESTIGATORS)

9. PROJECT DESCRIPTION

Objectives: The first objective is an extension of methods recently developed for the identification of peptides present in urine, blood, and other tissues to allow quantitation for normal and cancerous subjects. The ultimate objective is increased understanding of the role of peptides in protein synthesis, especially in terms of the synthesis of tumor proteins, and in the kinetics of nitrogen metabolism.

Methods Employed: Body fluids and tissue extracts are treated by different fractionation procedures to remove protein and other constituents, leaving the peptides in solution. These solutions are further fractionated by means of chromatographic and electrophoretic procedures. By means of chromatography, paper electrophoresis, end-group analyses and conventional methods of organic chemistry, identification and quantitation is effected. By means of regular seminar meetings (7 people), consideration of nitrogen metabolism of the whole organism is being made by setting up theoretical models, developing differential equations on the basis of the models, and making comparisons of different models utilizing available experimental data. Particular attention is being paid to cancer subjects.

Major Findings: Theoretical calculations of R_f values of peptides, based on the free energy relationships for the phases of chromatographic solvents (method of Pardee) have been made for over 75 peptides for 9 solvent systems. Comparison of these theoretical R_f values with the observed values obtained in a study of over 75 synthetic peptides in 15 solvent systems showed that the observed and calculated values agree, with nearly every peptide, within approximately 0.10 R_f. In the work on isolation of peptides from

large volumes of urine, the difficulties resulting from large amounts of salt have been overcome by the use of 4% cross-linked Dowex 50, allowing the peptides to be selectively eluted. Separation of the peptides by column chromatography, even when gradient elution was employed, was difficult, and paper electrophoresis combined with chromatographic procedures has permitted the isolation of several components giving only a single spot on paper chromatograms. After hydrolysis these components have given from one to eight spots, and the following peptides have been identified tentatively (no order for the amino acids has yet been established): [Asp, Gly] (and probably also its isomer since different fraction from a column gave the same two amino acids); [Glu, Gly, Ser]; [Ala, Glu, Gly, Ser] (also found in two other different fractions); [Glu, Asp, Gly]; [Glu, Gly]; [Ala, Glu, Gly, Ser, Asp, Leu, Phe]; [Glu, Gly, Asp, Val, Leu, Ser, Ala, Phe]. The amino acids that appeared in greatest amounts were Glu, Asp, and Gly. When the urine from a patient with multiple myeloma was deproteinized by heat treatment, many glycyl-peptides were found, but when deproteinization was effected by treatment with ethanol in the cold, only a few glycyl-peptides were found. Preliminary fractionation of plasma and pleural effusion fluid indicates peptides can be demonstrated in these materials if large enough samples are employed. In the open system kinetics seminar (Cornfield, Greenhouse, Schneiderman, Mantel, Tschudy, Steinfeld, and Baker), rate constants for nitrogen metabolism in the human organism based on one type of model have been calculated, and more complicated models have been devised and differential equations developed for these models. The equations describing a model with an infinite number of metabolic pools have been developed by the mathematicians and prove to be in a form easily handled.

Significance to Cancer Research: Peptides and amino acids, which are obtained from the partial degradation of protein, appear to be involved in the synthesis of protein, and reports in the literature indicate an increase of peptides in the blood of cancer patient. It is expected that studied on peptides will be of value for understanding protein structure and the mechanism of protein synthesis; it is supposed that an understanding of protein synthesis will be of value in understanding the functioning of cancer cells; it is believed that an understanding of the functioning of cancer cells will be of value in providing a basis for chemotherapy; it is hoped that chemotherapy will be of value in the treatment of cancer.

Proposed Course of Project: The work on peptides, although numerous fractions from urine, plasma, pleural effusion fluid, and B. subtilis culture media have been prepared by chromatographic procedures, will be pursued at a greatly diminished rate since Dr. Moore will be spending a good portion of his time on protein fractionation and the principal investigator will not be doing laboratory investigation. It is expected that the seminar group will continue to meet to discuss open system kinetics, and it is

hoped that sufficient data will become available to allow pertinent calculations to be made with the theoretical derivations.

10. NCI-315
SERIAL NO.

11.
BUDGET ACTIVITY:

RESEARCH	[x]	ADMINISTRATION	[ ]
REVIEW AND APPROVAL	[ ]	TECHNICAL ASSISTANCE	[ ]

NO ENTRIES FOR ITEMS 12, 13, AND 14.

15.
PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1955

In preparation.

16.
HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1955

The principal investigator is continuing his terms of office as Secretary of the Division of Biological Chemistry of the American Chemical Society and as a member of the Editorial Board of the Journal of the National Cancer Institute. He was also elected into the American Association of Biological Chemists and the American Association for Cancer Research.

PROJECT REPORT FORM

1. CI / NSTITUTE — 2. Laboratory of Biochemistry / LABORATORY OR BRANCH

3. linical Biochemical Research / ECTION OR SERVICE — 4. -------- / LOCATION (IF OTHER THAN BETHESDA) — 5. NCI-316 / SERIAL NO

6. tudies of Mutant Forms of Hemoglobin / ROJECT TITLE

7. I. A. Itano / RINCIPAL INVESTIGATOR(S)

8. -------- / THER INVESTIGATORS

9. ROJECT DESCRIPTION

Objectives: To apply the methods of physical chemistry to the identification, fractionation, and characterization of abnormal human hemoglobins. To develop new methods to attain these ends.

Methods Employed: Electrophoresis by the moving boundary and zone methods. Solubility determinations in concentrated salt solutions. Spectrophotometric determinations of rates and mechanisms of hemoglobin denaturation in alkali.

Major Findings: Discovery of an eighth inherited abnormal human hemoglobin (J). Mobilities of normal and abnormal hemoglobins (A-J) in univalent buffers. Relationship of abnormal hemoglobin metabolism to human disease in terms of their relative rates of synthesis.

Significance to Cancer Research: One approach to the cancer problem is the study of mutations. The abnormal hemoglobins result from mutant genes in humans, and the elucidation of the properties and structures of these hemoglobins may shed some light on the underlying basis of mutations.

Proposed Course of Project: Continuation of basic research along the lines outlined above. Continued collaboration in clinical research with internists, pediatricians, and hematologists interested in the abnormal hemoglobin problem.

PROJECT REPORT FORM (Cont'd)

10. NCI-316
SERIAL NO.

11.
BUDGET ACTIVITY:

RESEARCH	[x]	ADMINISTRATION	[ ]
REVIEW AND APPROVAL	[ ]	TECHNICAL ASSISTANCE	[ ]

NO ENTRIES FOR ITEMS 12, 13, AND 14.

15.
PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALEND. YEAR 1955

1. P. Sturgeon, H. A. Itano, and W. R. Bergren, Clinical Manifestations of Inherited Abnormal Hemoglobins: I. The Interaction of Hemoglobin-S with Hemoglobin-D. II. Interaction of Hemoglobin-E with Thalassemia Trait. Blood, 10, 389-404 (1955

2. P. Strugeon, H. A. Itano, and W. R. Bergren, Genetic and Biochemical Studies of "Intermediate" Types of Cooley's Anemia Brit. J. Hemtaology, 1, 264-277 (1955).

3. H. A. Itano, Clinical States Associated with Alterations of the Hemoglobin Molecule. A.M.A. Arch. Int. Med., 96, 287-297 (1955).

16.
HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1955

H. A. Itano - Delivered the George Minot Lecture for the Section on Experimental Medicine and Therapeutics of the American Medical Association on June 18, 1955.

PROJECT REPORT FORM

1. NCI
INSTITUTE

2. Laboratory of Biochemistry
LABORATORY OF BRANCH

3. Clinical Biochemical Research
SECTION OR SERVICE

4. ---------
LOCATION (IF OTHER THAN BETHESDA)

5. NCI-317
SERIAL NO

6. Glutamine Metabolism
PROJECT TITLE

7. A. Levintow and A. Meister
PRINCIPAL INVESTIGATOR(S)

8. J. F. Downey and P. Abendschein
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: This project seeks the elucidation of the role of glutamine and related compounds in the metabolism of normal and neoplastic tissues.

Methods: Soluble enzymes are extracted and purified from normal and neoplastic tissues and the reactions catalyzed by these enzymes are studied in vitro, using spectrophotric, chromatographic, and other techniques. Substrates are prepared by organic chemical procedures and rigorously characterized. These approaches are supplemented by the use of isotopically labelled compounds.

Major Findings: 1. Studies with a highly purified enzyme which catalyzes the synthesis of glutamine from glutamic acid, ATP, and ammonia have been continued. This reaction has been studied in collaboration with G. H. Hogeboom and E. L. Kuff of the Laboratory of Biology by means of ultracentrifugation and a powerful new sampling procedure developed by these workers. Convincing evidence has been adduced that glutamine synthesis and glutamyl transfer are both catalyzed by the same monodisperse enzyme. Nevertheless the latter is not merely the manifestation of reversal of the former. This leads to a principle of some significance; namely, that an enzyme which catalyzes synthesis of an amide bond also catalyzes a transpeptidation reaction.

2. Procedures for isolation of glutamine from enzymatic reaction mixtures have been developed. These procedures provide convenient methods for the preparation of isotopically labelled glutamine.

3. The role of glutamine in the biological economy of the human cervical carcinoma cell (HeLa) is being investigated in collaboration with H. Eagle of NMI. Glutamine is an essential requirement

for the cultivation of this cell in tissue culture. The metabolic role of glutamine is being studied by means of isotopically labeled glutamine prepared as in (2) above. Preliminary results indicate that glutamine is specifically used with extraordinary economy in the synthesis of protein and nucleic acid.

4. Studies on the mechanism of the enzymatic synthesis of the amide bond of glutamine have been continued. The role of γ-glutamyl phosphate has been investigated by the synthesis and study of the more stable derivative N-acetyl-γ-glutamyl phosphate. Studies with this compound using amino acid acylase indicate that γ-glutamyl phosphate per se is probably not involved in the enzymatic synthesis of glutamine.

Significance to Cancer Research: We interpret recent findings as strong evidence that glutamine is an important intermediate not only in amino acid and peptide metabolism, but in purine synthesis as well. Study of a compound which may stand at the crossroads leading to proteins on the one hand and to nucleic acids on the other would appear to offer unique opportunities for the elucidation of possible interrelationships of these two classes of compounds, each of which plays a basic role in growth processes. It is of importance that folic acid or a related compound is required for purine synthesis. This aspect of the problem and the effect of antifolic acid derivatives are of great interest in this work, and may lead to important relationships significant to the conduct of clinical chemotherapeutic experiments.

Proposed Course of the Project: The principal project contemplated is further study of glutamine metabolism in the HeLa carcinoma cell in tissue culture.

PROJECT REPORT FORM (Cont'd)

10 NCI-317
SERIAL NO.

11 BUDGET ACTIVITY:

RESEARCH	[x]	ADMINISTRATION	[ ]
REVIEW AND APPROVAL	[ ]	TECHNICAL ASSISTANCE	[ ]

NO ENTRIES FOR ITEMS 12, 13, AND 14.

15 PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1955

1. A. Meister, L. Levintow, R. E. Greenfield, and P. A. Abendschein, Hydrolysis and Transfer Reactions Catalyzed by Omega-amidase Preparations. J. Biol. Chem., 215, 441 (1955).

2. L. Levintow, A. Meister, G. H. Hogeboom, and E. L. Kuff, Studies on the Relationship of the Enzymatic Synthesis of Glutamine and the Glutamyl Transfer Reaction. J. Am. Chem. Soc., 77, 5304 (1955).

16 HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1955

None

PROJECT REPORT FORM

1. NCI — INSTITUTE
2. Laboratory of Biochemistry — LABORATORY OR BRANCH
3. Enzymes and Metabolism — SECTION OR SERVICE
4. --------- — LOCATION (IF OTHER THAN BETHESDA)
5. NCI-318 — SERIAL NO.

6. Comparative studies on the metabolism of catalase and other heme proteins in normal and tumor-bearing animals.
PROJECT TITLE

7. Drs. Robert E. Greenfield and Vincent E. Price
PRINCIPAL INVESTIGATOR(S)

8. None
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: To study and compare the relative rates of incorporation of radioactive iron into the ferritin, catalase, and hemoglobin of normal and tumor-bearing animals.

Methods Employed: Comparative time studies were made to follow the rate of incorporation of Fe^{59} into the ferritin catalase, and hemoglobin of normal and tumor-bearing animals. Ferritin, catalase, and hemoglobin were isolated at the various time intervals and their specific radioactivities determined. Measurements of blood volume, hemoglobin, hematocrit, liver catalase activity, and of iron in the various body pools were carried out to assist in evaluation of the radioactive tracer data. An inbred strain of rats was used to reduce random variation and to make any differences observed between normal and tumor-bearing rats more definitely significant.

Major Findings: 1) The tumor-bearing animals had anemia, lowered liver catalase, and a lowered amount of storage iron in the liver. 2) In the tumor-bearing animals there was an increased rate of incorporation of iron into the erythrocytes, and a decreased uptake into liver ferritin and liver catalase. The uptake into liver catalase appeared to parallel that into liver ferritin. 3) The tumor-bearing animals were found to have a large pool of iron in the tumor, considerably larger in amounts than the iron pool of the liver, which is the major iron storage organ of the body.

Significance to Cancer Research: The anemia and lowered liver catalase of tumor-bearing animals indicate that there is a derangement of iron metabolism in these animals. It is important in an understanding of this derangement to determine whether the anemia and lowered liver catalase are directly related to a common derangement or whether the tumor interferes with the metabolism of each by separate mechanisms.

Proposed Course of Research: The finding of a large pool of iron in the tumor has led to studies on the rapid destruction and fate of erythrocytes in tumor-bearing animals, and to a study of the several factors involved

No. 9 cont'd. NCI-318

in the anemias of these animals. Because of their importance separate projects have been established concerning these studies. Further work in the metabolism of liver catalase will be carried on with the following objectives in mind: 1) What, if any, is the relationship between the metabolism of catalase and liver ferritin. 2) What, if any, is the relationship between the metabolism of catalase and the anemia of tumor-bearing animals. 3) Does the tumor produce a factor which acts directly and specifically to interfere with iron or porphyrin metaboli in the liver of tumor-bearing animals. If so, what precursors accumulate, and what is the rate of incorporation of isotope into the iron, porphyrin, and protein moieties of catalase before and after removal of the tumor.

PROJECT REPORT FORM (CONT'D)

10. NCI-318
SERIAL NO.

11.

BUDGET ACTIVITY:

RESEARCH [x] ADMINISTRATION [ ]

REVIEW AND APPROVAL [ ] TECHNICAL ASSISTANCE [ ]

NO ENTRIES FOR ITEMS 12, 13, AND 14.

15.

PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1955.

None

16.

HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1955.

None

PROJECT REPORT FORM

1. NCI — INSTITUTE
2. Laboratory of Biochemistry — LABORATORY OR BRANCH
3. Enzymes and Metabolism — SECTION OR SERVICE
4. ---------- — LOCATION (IF OTHER THAN BETHESDA)
5. NCI-319 — SERIAL NO.

6. Studies on the Catalase-reducing Factor in Tumors
PROJECT TITLE

7. Mr. William R. Sterling
PRINCIPAL INVESTIGATOR(S)

8. Drs. Vincent E. Price and Robert E. Greenfield
OTHER INVESTIGATORS

9 PROJECT DESCRIPTION:

Objectives: To identify a factor in tumors, or in the blood or urine of cancer patients. which lowers the liver catalase when injected into normal mice.

Methods Employed: 1) Preparation of fractions from urine by the method of Nakagawa (Tokyo Imperial Academy, Japan, Proceedings 28, 305-310, 1952), with minor modifications. 2) Assay of the various fractions in an inbred strain of mice using serial logarhythmic dilutions. 3) Calculation of the median effective dose, which is the amount of a given fraction required to give half the maximal effect. 4) Comparison of similar fractions obtained from the urine of cancer patients and from normal humans.

Major Findings: 1) The findings of Nakagawa have been in general confirmed except as to the magnitude of the effect produced by the urine fractions. Nakagawa reported an average lowering of 47 percent of the liver catalase activity of mice which had been injected intraperitoneally with the urine fractions of cancer patients, as compared with the liver catalase activity of mice injected with fractions obtained from the same amount of normal urine. In our hands the average maximal lowering has been 25 to 30 percent and in no case has it exceeded 35 percent regardless of the dose administered. Injection of saline alone gives a lowering of 10 to 15 percent. 2) The catalase reduction may also be produced by fractions from some normal urines but there is much less of this fraction in normal urine. The material that is there is, however, as active as that found in urine from cancer patients in terms of specific activity, i.e. the inhibition produced per mgm. of material injected.

Significance to Cancer Research: If a factor can be found in the urine or blood of cancer patients which acts specifically to interfere with a metabolic system of a test animal it might have great value in a diagnostic test for cancer. A study of its production by the tumor would be of considerable importance in understanding tumor metabolism.

No. 9 cont'd. NCI-319

Proposed Course of Research: Since the maximal effect found by the urine fractions produced an inhibition of catalase activity of only 30 percent it seems likely that the effect on catalase is secondary to some other metabolic effect produced by the urine factor. Until the nature of such a primary effect can be determined further study of the urine factor does not appear fruitful at this time. The maximal effect produced by the urin fractions on the liver catalase activity of mice is too small for an effective bioassay.

Further studies on the catalase-reducing factor will involve tumors direct where fractions giving a considerably greater effect can be obtained.

cont'd.

NCI-319

Proposed Course of Research: Since the maximal effect found by the urine fractions produced an inhibition of catalase activity of only 30 percent it seems likely that the effect on catalase is secondary to some other metabolic effect produced by the urine factor. Until the nature of such a primary effect can be determined further study of the urine factor does not appear fruitful at this time. The maximal effect produced by the urine fractions on the liver catalase activity of mice is too small for an effective bioassay.

Further studies on the catalase-reducing factor will involve tumors directly where fractions giving a considerably greater effect can be obtained.

PROJECT REPORT FORM

1. NCI 2. Laboratory of Biochemistry
INSTITUTE LABORATORY OR BRANCH

3. Enzyme and Metabolism 4. ------- 5. NCI-320
SECTION OR SERVICE LOCATION (IF OTHER THAN BETHESDA) SERIAL NO.

6. Isolation and Characterization of Liver Catalase of Normal and Tumor-bearing Animals.
PROJECT TITLE

7. Drs. Robert E. Greenfield and Vincent E. Price
PRINCIPAL INVESTIGATOR(S)

8. None
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION:

Objectives: 1) Localization of catalase in the particulate fractions of rat liver. 2) Electrophoretic studies on catalase from normal and tumor-bearing animals.

Methods Employed: 1) Isolation of catalase from particulate fractions using sucrose and the high polymer, polyvinylpyrrolidone, to protect the integrity of the mitochondria. 2) Electrophoretic studies on very pure fractions of catalase from normal and tumor-bearing animals to see if any difference in the electrophoretic mobilities can be observed.

Major Findings: 1) See 1954 Annual Report. The work of Objective 1 was essentially accomplished in 1954 and is now in press. See Item 14, below. 2) The work of Objective 2 has not developed as our attention has been drawn into other aspects of iron-metabolism in tumor-bearing animals.

Significance to Cancer Research: See 1954 report.

Proposed course of project: It is not expected to pursue this project further at this time. The findings reported will be used in other aspects of this work as it develops.

PROJECT REPORT FORM (CONT'D)

10. NCI-320

SERIAL NO.

11.

BUDGET ACTIVITY:

RESEARCH	[x]	ADMINISTRATION	[ ]
REVIEW AND APPROVAL	[ ]	TECHNICAL ASSISTANCE	[ ]

NO ENTRIES FOR ITEMS 12, 13, 14.

15.

PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 19

1. Liver Catalase III. Isolation of Catalase from Mitochondrial Fractions of Polyvinylpyrrolidone-sucrose Homogenates. Journal of Biological Chemistry. In press.

16.

HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1955.

None

PROJECT REPORT FORM

1. NCI 2. Laboratory of Biochemistry
INSTITUTE LABORATORY OR BRANCH

3. Enzymes and Metabolism 4. ---------- 5. NCI-322
SECTION OR SERVICE LOCATION (IF OTHER THAN BETHESDA) SERIAL NO.

6. Preparation and purification of cathepsins and nucleases from normal and neoplastic tissues
PROJECT TITLE

7. Dr. Mary E. Maver
PRINCIPAL INVESTIGATOR(S)

8. Miss Antoinette Greco
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION:

Objectives: The objective of this project is to separate the closely associated nuclease and proteinase systems of normal and neoplastic tissue.

Methods employed: The tissues are homogenized and subjected to centrifugation, ammonium sulfate precipitation at different hydrogen ion concentrations, dialysis and repeated precipitation in cold alcohol. After lyophilization the purified factions are subjected to chromatographic separation. The rates of splitting rat liver ribonucleic acid were compared.

Major Findings: The rate of activity of the ribonuclease (RNase) and desoxyribonuclease (DNase) preparations from the two hepatomas used was much higher than those of the normal liver. The hepatic tissues show two pH optima and the purified preparations have RNase activity which is not sensitive to heating. It was possible by a chromatographic technique (with Drs. Sober and Peterson) to separate two RNases in purified fractions from calf spleen.

Significance to Cancer Research: A study of the enzymes involved in nucleic acid and protein metabolism is important to an understanding of tumor growth. The exact role of the enzymes being studied in tumor metabolism remains to be determined.

Proposed Course of Project: It is proposed to characterize the purified cathepsin preparations from normal and neoplastic tissues by their activities on hemoglobin and several synthetic peptides. Transpeptidase activities particularly will be studied. The chromatographic separation of the enzymic activities of spleen and liver will be continued, and the activities of the RNases on cyclic nucleotides will be compared.

PROJECT REPORT FORM (CONT'D)

10. NCI-322

SERIAL NO.

11.

BUDGET ACTIVITY:

RESEARCH	[x]	ADMINISTRATION	[ ]
REVIEW AND APPROVAL	[ ]	TECHNICAL ASSISTANCE	[ ]

NO ENTRIES FOR ITEM 12.

13.

IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

Dr. Leon Heppel of N.I.A.M.D. is using various enzymes to determine the structure of ribonucleic acid. He has used our purified spleen ribonuclease in the course of their studies and finds it different from the one he has prepared. Our objective has been a comparison of the ribonucleases from normal and neoplastic tissues.

NO ENTRIES FOR ITEMS 14, 15, AND 16.

PROJECT REPORT FORM

1. NCI 2. Laboratory of Biochemistry
INSTITUTE LABORATORY OR BRANCH

3. Enzymes and Metabolism 4. - - - - - - 5. NCI-323
SECTION OR SERVICE LOCATION (IF OTHER THAN BETHESDA) SERIAL NO.

6. Chemical Composition of C3H Hepatomas as Related to Growth and Transplantability
PROJECT TITLE

7. Mary E. Maver, H. B. Andervont, Robert Koegel
PRINCIPAL INVESTIGATOR(S)

8. Antoinette E. Greco
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objective: To determine whether differences in chemical composition, as determined by content of water, total lipid, N, P, K and Na, can be correlated with differences in the growth rates of the tumors or in their ability to grow when transplanted.

Methods employed: The water content of the tumors was determined by weighing them before and after removal of water by lyophilization. The lipid content was determined by continuous extraction of the powdered, dried tumors with mixtures of alcohol and ether and of chloroform and methyl alcohol in a microsoxhlet apparatus. The N and P were determined by the usual micro-techniques. The Na and K were determined by use of the flame spectrophotometer. Because of possible variations in chemical composition of tumors with differing etiology the study was confined to the spontaneous hepatomas in C3H male mice.

Major Findings: Six spontaneous C3H hepatomas have been transplanted. Two of these spontaneous tumors arose in different lobes of the liver of one mouse. Six different types of growth have been represented by the original six hepatomas. One has failed to grow on transplantation, one has grown very slowly, one has changed to a sarcoma, 2 have grown well on transplantation and one less well. Enough material has been collected for an initial evaluation of this approach and no further tumors are being transplanted. Final chemical analyses are being made on the tissues collected from a total of 130 mice.

Significance to Cancer Research: This study will add to our basic knowledge concerning the chemical properties of tumors. Very few, if any, studies of this type using inbred mice and the latest techniques for sodium and potassium analyses have been reported. Results of the chemical analyses of the original tumors and of their transplants may indicate what chemical conditions are present in a readily transplantable, fast growing tumor. It has been suggested that similar

No. 9 cont'd. NCI-323

chemical analyses of human tumors after surgery might furnish a prognosis as to the rate of growth and malignancy of subsequent metastase.

Proposed Course of Project: The collected tumor tissues will be analyzed chemically. The results will be arranged for statistical study and final evaluation. Further studies will be dependent upon the results of this evaluation.

PROJECT REPORT FORM (CONT'D)

10. NCI-323
SERIAL NO.

11.

BUDGET ACTIVITY:

RESEARCH	[x]	ADMINISTRATION	[ ]
REVIEW AND APPROVAL	[ ]	TECHNICAL ASSISTANCE	[ ]

NCENTRIES FOR ITEMS 12, 13, 14, 15, AND 16.

PROJECT REPORT FORM

1. NCI 2. Laboratory of Biochemistry

3. Nutrition and Carcinogenesis 4. - - - - - 5. NCI-324

SECTION OR SERVICE LOCATION (IF OTHER THAN BETHESDA) SERIAL NO.

6. Biological studies of the mechanism carcinogenesis

PROJECT TITLE

7. H. P. Morris

PRINCIPAL INVESTIGATOR(S)

8. Billie P. Wagner, Dr. C. A. Velat, and Dr. L. S. Lombard

OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objective: Testing for carcinogenicity of compounds excreted in the urine of rats ingesting chemical carcinogens such as 2-AAF (2-acetylaminofluorene) or of other possible degregation products of 2-AAF. The carcinogenic activity of these metabolites or possible metabolites is expected to help explain how different chemical groups alter the carcinogenic picture and provide leads for studying their intermediary metabolism. A preliminary study of one compound requires approximately two or more years to complete so that there is an overlapping of these studies from one annual report to the next.

Methods employed: Known chemical compounds are incorporated into the diet of suitable strains of rats. Usually after a test period of 12-18 months or sooner if death appears imminent the animals are carefully necropsied, the tissues fixed, sectioned, stained, and finally examined microscopically for evaluation of tissue changes produced by the chemical under study.

Results: The discovery of a chemical (4' fluoro-4-acetylaminobiphenyl) causing kidney tumors in rats was 1st made in this laboratory and later confirmed by other investigators. One effort this year has been the study of the induction and histogenesis of kidney tumors in the rat by 4' fluoro-4-acetylaminobiphenyl. While this compound is not specific for the induction of kidney tumors it does produce a much higher incidence of such tumors in rats than anyother known drug. One possible metabolite of 2-AAF 3,4-xylidine, a dimethylaromaticamine, and one of the simplest aromatic amines which we have discovered to be carcinogenic was studied during the year. A very high percentage of pituitary tumors have been found in rats ingesting this compound. Two other aromatic amines which might be produced if the fluorene nucleus of 2-AAF was broken during metabolism are being tested for carcinogenic activity namely p-fluoroacetanilide, and orthohydroxacetanilide. Two metabolites isolated from the urine of rats ingesting 2-AAF namely 2-acetyl-amino-7-OH-fluorene and 2-acetylamino-

No. 9 cont'd. NCI-324

5-OH-fluorene are currently being fed to rats to compare their carcinogenic potency with 2-AAF. Additional animal experiments were carried out with Buffalo and AxC strain rats ingesting 2-AAF and 2,7-diAAF in order to provide more and better material for estimating tumor incidence and distribution and for determining the influence of age of starting female rats on the incidence of liver tumors.

Significance to Cancer Research: The intimate mechanism by which a carcinogenic agent of known structure brings about a neoplastic change is a present obscure. The carcinogenic potency of chemical compounds which may be produced in vivo during metabolism of chemical carcinogens or related to structural changes which the chemicals may undergo during passage through the animal forms an important part of studies on possible mechanisms of carcinogenesis. New Pathways of metabolism may result from compounds which have high specific activity for certain organs or tissues and provide new points for attacking the intermediary metabolic processes which occur in the animal prior to the detection of a definitive tumor. It is expected such studies will aid in a better understanding of the cause of cancer.

Proposed course of project: The possible estrogenic activity of 3,4-xylidine will be studied. Additional compounds will be given a preliminary test as they become available. Refinements in the testing of a few of the more important ones will be carried out and the material nearing completion will be prepared for publication.

PROJECT REPORT FORM (CONT'D)

10. NCI-324

SERIAL NO.

11.

BUDGET ACTIVITY:

RESEARCH	[x]	ADMINISTRATION	[ ]
REVIEW AND APPROVAL	[ ]	TECHNICAL ASSISTANCE	[ ]

NO ENTRIES FOR ITEMS 12, 13, AND 14.

15.

PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1955.

1. Hepatocarcinogenesis by 2-acetylaminofluorene and related compounds including comments on dietary and other influences, Harold P. Morris J. Nat. Cancer Inst., Suppl. 15: 1535-1545, 1955.

16

HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1955.

None

PROJECT REPORT FORM

1. NCI 2. Laboratory of Biochemistry
INSTITUTE LABORATORY OR BRANCH

3. Nutrition and Carcinogenesis 4. - - - - - - - 5. NCI-325
SECTION OR SERVICE LOCATION (IF OTHER THAN BETHESDA) SERIAL NO.

6. Mechanism of Carcinogenesis: Investigation of the metabolism of acetylaminofluorene and related compounds
PROJECT TITLE

7. Helen M. Dyer
PRINCIPAL INVESTIGATOR(S)

8. Harold P. Morris
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objective: To accumulate information on the effects of a chemical carcinogen on the metabolic activities of the host and the action of the host upon the carcinogen with the hope of learning something to explain the mechanism of carcinogenesis. Specifically: continued study of compounds structurally related to 2-acetylaminofluorene (2-AAF), and a new approach to a related problem; an attempt to explain why 2-AAF induces liver tumors in a given casein-containing diet and under the same experimental conditions induces bladder tumors if hydrolyzed casein and DL-tryptophan are substituted for casein.

Methods Employed: Continued use of isotopic nitrogen as a tracer and of the two diazotization methods for the quantitative determination of the excretory material after administration of the compounds to rats.

The adaptation of Eckert's photometric methods for the separate determinations of tryptophan, kynurenine, and anthranilic acid in the urine of rats receiving casein or hydrolyzed casein diets with and without supplements of 2-AAF, and with (and in the case of the casein diet also without) supplements of L- or D-tryptophan.

Use of paper chromatography and identification of possible metabolites by ultraviolet irradiation and by staining with p-dimethylaminobenzaldehyde.

Two different methods are being used for the removal of ammonia nitrogen, aliphatic amines and non-tryptophan-like indoles and for concentration of the metabolites in the urine, one method of ion exchange with treated permutit which does not adsorb tryptophan-like compounds, the other with deactivated carbon to adsorb aromatic indoles which are subsequently eluted with dilute phenol. Both methods are followed by concentration by distillation at reduced pressure. The urine is used with and without preliminary digestion with bacterial B-glycuronidase.

No. 9 cont'd. NCI-325

Major Findings: 1) The first study of excretory products from 2-AF and related compounds was completed a year ago and a paper was published on this phase of the work as shown in itme 15.

2-Acetylamino-7-methoxyfluorene, administered to rats by stomach tube in equilmolar amounts to that used for 2-AAF showed similar excretory behavior to 7-OH-2-AAF. Only traces of diazotizable material could be detected in acetone extracts of the feces, whereas the urinary diazotizable-R-salt-reacting material, calculated as 7-methoxy-2-AAF following acid hydrolysis accounted for 72 percent of that administered. By the nitrite test, in which 7-methoxy-2- AF-HCl and 7-methoxy-2-AF were found to behave like 7-OH-2-AAF after hydrolysis of the latter, 80 percent of the material administered as 7-methoxy-2-AAF could be accounted for in the urine if calculated as 7-OH-2-AAF. Not more than 5 percent of the recovered material was present as free amine. The findings suggest that 7-methoxy-2-AAF may be converted in the rat to 7-OH-2-AAF and thus have the same fate as the latter. If this is so the compound would be expected to be less carcinogenic to rats than 2-AAF.

2) In a continuation of studies of protein binding of isotopic nitrogen the following observations have been made: After administration of 2-diacetylaminofluorene-N^{15} or of 2-nitrofluorene-N^{15} to rats under the same experimental conditions as were used for 2-AAF-N^{15} the same amount of isotopic nitrogen enrichment of the crude protein fractions from the livers was found as with 2-AAF. The N^{15}-binding by liver proteins in the case of these two compounds, both of which have been found by Dr. Morris to be carcinogenic, may be a result of a common metabolic pathway with 2-AF and/or 2-AAF.

4-AAF, on the other hand, which has been found by Morris to be little, if at all carcinogenic, showed no protein binding under the same experimental conditions.

Dialysis of acetate-buffer homogenates for 3 days at 9 deg.C. had no effect on the amount of isotopic nitrogen enrichment of the subsequently isolated crude protein fractions but dialysis did result in a decrease in the amounts of the proteins recovered, especially in the fractions obtained by coagulation of the supernatant of the centrifuged dialyzed material.

3) In the preliminary investigation of a possible relation between the difference in behavior of 2-AAF with the hydrolyzed casein diet supplemented with tryptophan, and the casein diet, no significant differences in indole metabolites have been found by the photometric methods of analysis, nor by paper chromatography nor has any difference been observed between the same diets with and without 2-AAF supplements. There is some evidence that more free tryptophan is excreted in the urine of the rats receiving D-tryptophan supplements than with the other diets, including those with L-tryptophan supplements.

With paper chromatography, resolution of the concentrates from the urine has been good, resulting in fourteen distinguishable spots. They are almost identical in the urines from all 7 of the dietary combinations. Attempts are now being made to identify the spots. Following glucuronidase digestion of the urine, the same number of spots is observed but the spots have different R_f values.

The diazotization-R-salt treatment of the urines before and after mild acid hydrolysis, and the "nitrite" test for 7-OH-2-AAF revealed no differences with the different diets in the amounts of total diazotizable, free and conjugated diazotizable amines, or hydroxylated aminofluorenes that could be detected by the methods.

Through the first 9 weeks of feeding, some interesting observations have been made on the total amounts of indole-reacting urinary material, the nitrogen excretion and weight changes in the different groups of rats. Whether or not these differences with the different diets reflect a difference in metabolism of the tryptophan or of the 2-AAF is not known. They are, however, suggestive of some influence of the diet.

Significance to Cancer Research: It is hoped that any information obtained on the action of the animal on a carcinogen or of the carcinogen on the normal metabolic reactions of the animal may throw some light on the understanding of the mechanism of carcinogenesis. Since diet is obviously involved in the site of the tumor induced by 2-AAF in casein and hydrolyzed casein-tryptophan-supplemented diets, it is possible that identification of the metabolites excreted may give a clue to metabolic differences operating in the animal under the different dietary conditions.

Proposed course of project: Further attempts will be made to identify urinary metabolites that may be present in trace amounts by pooling the urines of 8 rats instead of 2 rats as has been done previously with the casein and hydrolyzed casein tryptophan diets. The urine will be examined at intervals up to the time of the appearance of tumors.

A comparison of the metabolism of L- and D-tryptophan in the rat in the presence of AAF will be made using the 2-AAF basal diets without supplements of tryptophan during the collection period and administering the amino acid by stomach tube. The excretory products from tryptophan and from 2-AAF will be investigated.

A comparison will be made of the distribution of urinary nitrogen in addition to the total N with the different diets, especially the ammonia N, urea N and creatinine N.

With Dr. Morris it is proposed to compare the urinary excretion of diazotizable-R-salt-reacting, and nitrite reacting, free and conjugated amines and the nitrogen binding by liver proteins of 2-AAF in intact and thyroidectomized rats.

PROJECT REPORT FORM (CONT'D)

10. NCI-325
SERIAL NO.

11.
BUDGET ACTIVITY:

RESEARCH	[x]	ADMINISTRATION	[ ]
REVIEW AND APPROVAL	[ ]	TECHNICAL ASSISTANCE	[ ]

NO ENTRIES FOR ITEMS 12, 13, AND 14.

15.
PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1955

A Comparison of the Patterns of Excretion and the Carcinogenicity in the Rat of 2-Acetylaminofluorene and Related Compounds. Helen M. Dyer, J. Nat. Cancer Inst., 16, 11-30, 1955.

16.
HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1955.

None

PROJECT REPORT FORM

1. NCI 2. Laboratory of Biochemistry
INSTITUTE LABORATORY OR BRANCH

3. Nutrition and Carcinogenesis 4. - - - - - - 5. NCI-327
SECTION OR SERVICE LOCATION (IF OTHER THAN BETHESDA) SERIAL NO.

6. Mechanism of Carcinogenesis - Metabolism of 2-Acetylaminofluorene and related compounds.
PROJECT TITLE

7 Dr. J. H. Weisburger and Dr. E. K. Weisburger
PRINCIPAL INVESTIGATOR(S)

8 P. H. Grantham and Dr. H. P. Morris
OTHER INVESTIGATORS

9 PROJECT DESCRIPTION

Objective: Study of the mechanism of the initiation of the neoplastic process using synthetic carcinogens such as 2-acetylaminofluorene as a tool. A number of approaches are followed: 1) The metabolism and the interaction of the carcinogen with body constituents are investigated; 2) The biological effect is correlated with chemical structure of potential carcinogens in order to understand structural requirements; 3) The carcinogenic action of known metabolites of a carcinogen is determined.

Methods: 1) By means of a radioactive tag at a stable position in a molecule, such as labeling carbon no. 9 of 2-acetylaminofluorene with the isotope carbon 14 the fate of the compound and its interaction with tissues can be traced completely. 2) Metabolic products in excreta or tissues are isolated by suitable techniques, separated by extraction, paper or column chromatography, counter-current distribution, vacuum sublimation, fractional crystallizations or other pertinent processes. After purification identification is attempted on the basis of physical and chemical properties. 3) Organic compounds are synthesized by new organic procedures as required for the metabolic studies, or for investigations of the structural relationships leading to carcinogenicity. 4) Analytical and chromatographic methods applicable to the biochemical studies are devised.

Major Findings: 1) A technique for fractionating relatively large amounts of the ether soluble metabolic products of 2-acetylaminofluorene (2-AAF) on a column of silicic acid was developed. Indications were obtained for the presence of 1-2 further unknowns in the ether extract; the other components are known and were reported previously. 2) Dunning, et al. (Cancer Research 10, 454 (1950)) has shown that bladder tumors are obtained in rats when DL-tryptophan is added to a diet containing 2-AAF. These observations were confirmed by Boyland et al. (Brit. Jour. Cancer 8: 647 (1954). To investigate whether this shift in target organ is due to an alteration in the metabolism of 2-AAF, we have separated and

No. 9 cont'd.

estimated the metabolites of 2-AAF. It was found that 1% L-tryptophan in the diet does not significantly alter the metabolism of 2-AAF.

3) To test the hypothesis that 2-acetylamino-1,-3,-5, and -7-hydroxy-fluorene were the only monohydroxylat products of 2-AAF metabolism the corresponding -8-hydroxy derivative was prepared in seven steps from fluoranthene. Metabolism experiments now underway will decide the issue. 4) It was found that a possible metabolite, 4-acetylaminobiphenyl-2-carboxylic acid, was not present in the urine of rats fed 2-AAF. 5) A large amount of the important 2-AAF metabolite, 2-acetylamino-5-hydroxyfluorene, was synthesized for biological testing by Dr. Morris. During one of the synthetic steps a new by-product in the form of 4-nitro-5-carboxyfluorene was isolated. Several derivatives, including the corresponding diamine, of possible interest in cancer research, were prepared. 6) During the synthesis of labeled 2-AAF-9-C^{14} for the metabolism work, a lead regarding the mechanism of the Wolff-Kishner reduction was obtained. A brief follow-up produced sufficient data for postulating a probable scheme. 7) A collection of infra-red spectra of fluorene derivatives and other compounds of interest in the biochemical work was started and a study of their interpretation was undertaken. During this work a correction was made in the assignment of the correct structure of 2-amino-5-nitrofluorene as compared to 2-nitro-5-aminofluorene It is hoped that an adequate understanding of infra-red spectra will further help the identification of unknowns both in our organic and our biochemical work.

Significance to Cancer Research: The disease can be reproduced at will by means of synthetic carcinogens such as 2-AAF. Therefore, this tool permits the investigation of the cause and origin of neoplasia leading to a understanding of the mechanism of this transformation. It follows that a rational attack on the prevention or cure of cancer can be devised once the basic process of its formation is clarified.

Proposed course of project: 1) Study of the isolation and characterization of the remaining unknown metabolites of the carcinogen 2-acetylaminofluorene (2-AAF). 2) Study of the metabolites of 2-AAF obtained from tissues such as liver and comparison with the urinary metabolites. 3) Study nature and variety of carcinogen-protein complexes with 2-AAF. 4) Study metabolites of 2-aminofluorene and compare to those of 2-AAF on the hypothesis that ortho-hydroxylated products may be increased. 5) Continuation of metabolic study regarding effect of tryptophan on 2-AAF induced bladder cancer and delay of liver carcinogenesis. D- and DL-tryptophan will be tested in addition to L-tryptophan. 6) Design experiments to test disturbance by 2-AAF of enzyme systems incorporating components of nucleic acids. 7) Organic chemical syntheses in support of main program above. 8) Analytical methodology in support of main program above.

PROJECT REPORT FORM (CONT'D)

10 NCI-327

SERIAL NO.

11

BUDGET ACTIVITY:

RESEARCH [X] ADMINISTRATION [ ]

REVIEW AND APPROVAL [ ] TECHNICAL ASSISTANCE [ ]

NO ENTRIES FOR ITEMS 12, 13, AND 14.

15

PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1955.

1. E. K. Weisburger: 2-Hydroxy-3-acetylaminofluorene, a Metabolite of 3-Acetylaminofluorene in the Rat, J. Am. Chem. Soc. 77 1914 (1955).

2. J. H. Weisburger: The Enzymic Deacetylation of the Carcinogen 2-Acetylaminofluorene and Related Compounds, Biochim Biophys. Acta 16, 382 (1955).

3. E. K. Weisburger and J. H. Weisburger: 2-Acetylamino-5-hydroxyfluorene, a Metabolite of the Carcinogen 2-Acetylaminofluorene. J. Org. Chem. 20, 1396 (1955).

16

HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1955.

Dr. E. K. Weisburger was appointed a member of the Program Committee of the Chemical Society of Washington, 1954-1955 and 1955-1956.

PROJECT REPORT FORM

1. NCI 2. Laboratory of Biochemistry
INSTITUTE LABORATORY OR BRANCH

3. Nutrition and Carcinogenesis 4. - - - - - - 5. NCI-328
SECTION OR SERVICE LOCATION (IF OTHER THAN BETHESDA) SERIAL NO.

6. Role of Iodine and Goitrogens in the Development and Growth of Thyroid Cancer
PROJECT TITLE

7. H. P. Morris
PRINCIPAL INVESTIGATOR(S)

8. H. J. Lipner (previous research fellow), B. P. Wagner and J. H. Weisburger
OTHER INVESTIGATORS

9 PROJECT DESCRIPTION

Objectives: To utilize the functional properties of thyroid tissue to concentrate and metabolize iodine in order to elucidate changes which occur during the progress from normal to neoplasia. Techniques of isotopic tracers provide sensitive methods of following functional changes occurring during the development and growth of thyroid tumors in experimental animals rather than relying on the conventional morphological criteria.

Methods Employed: Studies of iodine deficiency as a means of inducing transplantable tumors of the thyroid gland were in progress. Also the influence of light and diet on the uptake of I^{131} by the mouse thyroid gland was studied.

Major Findings: Transplants of hyperplastic thyroid tissue decreased by 50% in ability to concentrate iodine, which decrease was not due to transplantation of the tissue to another site per se. There was very little correlation between ability to concentrate I^{131} by these transplantable thyroid tissues and their morphological characteristics in different transplant generations.

Significance to Cancer Research: This is a direct approach with the use of a very sensitive technique to determine how this function of normal and cancer cells differ during the gradual course of developing into cancer cells. It is expected that these studies will evolve new understanding of how cancer cells loose some of their functional activities in becoming cancerous.

Proposed course of project: No new experiments are planned for the next year.

PROJECT REPORT FORM (CONT'D)

No. 9 cont'd. NCI-328

10. NCI-328
SERIAL NO.

11.

BUDGET ACTIVITY:

RESEARCH	[x]	ADMINISTRATION	[ ]
REVIEW AND APPROVAL	[ ]	TECHNICAL ASSISTANCE	[ ]

NO ENTRIES FOR ITEMS 12, 13, AND 14.

15.

PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1955.

1. The Experimental Development and Metabolism of Thyroid-gland tumors. Harold P. Morris, Advances in Cancer Research III pp 52-112 (1955).

2. Experimental Thyroid Tumors Harold P. Morris in "The Thyroid"- Brookhaven Symposia in Biology no. 7 pp 192-219 (1955).

3. The Effect of Propropylthiouracil on the Growth and Thyroid: Serum Iodide Ratio of Mouse Thyroid Antotransplants. H. J. Lipner, B. P. Wagner, and Harold P. Morris, Endocrinology 56: 606-607 (1955).

16.

HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1955.

None

PROJECT REPORT FORM

1. NCI — INSTITUTE
2. Laboratory of Biochemistry — LABORATORY OR BRANCH
3. Cytochemistry — SECTION OR SERVICE
4. -------- — LOCATION (IF OTHER THAN BETHESDA)
5. NCI-329 — SERIAL NO

6. Development of Unique Manometric and Electrochemical Methods of Measuring Gas Exchange in Cell Metabolism — PROJECT TITLE

7. D. Burk and G. Hobby — PRINCIPAL INVESTIGATOR(S)

8. ------- — OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: The development of simple, but unique methods for the determination of oxygen and CO_2/O_2 exchange ratios in metabolic studies of normal and neoplastic free cell suspensions in vitro.

Results: A simple manometric method has been developed for use in tissue or cell metabolism studies whereby simultaneous gas exchange measurements of both carbon dioxide and oxygen (and hence CO_2/O_2 quotient) can be made in acid media in a single standard Warburg manometric flask. The technique does not require eventual destruction of the system by the displacement of carbon dioxide with concentrated acids, or the complexity of apparatus typical of the Summerson differential method, or multiple-armed vessels as required in other methods, and it is possible to repeat experiments successively with the same biological material. In systems in which, for example, carbon dioxide is the substrate and oxygen is evolved, equilibration is carried out at an appropriate and known partial pressure of carbon dioxide. The known initial amount of CO_2 in the vessel, determined from the partial pressure, is allowed to be completely assimilated by the metabolic activity of the system. The pressure change of the manometer represents the net gas exchange of both the known and unknown gas. Oxygen is then determined from the net pressure change for both gases and the calculated pressure change for the known quantity of carbon dioxide consumed, employing appropriate predetermined vessel constants. The derived exchange quotient CO_2/O_2 is thence readily obtained by simple calculation.

No. 9 Continued. NCI-329

Further studies in the development and improvement of methods of oxygen gas detection and analysis in biological media, using galvanic cells having an iron anode and platinum-oxygen cathode, were directed towards obtaining greater electrode stability, linear response to oxygen over an extended range of oxygen tension above air saturation, and improvement of accuracy and response at these higher levels through newer methods of calibration. These studies involve electrical compensation methods, effects of micro-amounts of chelating agents in removing heavy metal ions from the platinum electrode surface, stabilizing effects on the cathode of thin membranous coatings of semi-permeable materials, and effects of physical treatment, such as heating and annealing of the platinum electrodes upon the stability of the system. A technique of electrode calibration for high oxygen concentrations, above 21%, in which the gas can be added to a completely closed liquid system, is under study, whereby oxygen released by the catalytic reduction of known concentrations of hydrogen peroxide is measured at the platinum electrode by corresponding changes in current output of the cell.

PROJECT REPORT FORM (Cont'd)

10. NCI-329
SERIAL NO.

11. BUDGET ACTIVITY:

RESEARCH	[x]	ADMINISTRATION	[ ]
REVIEW AND APPROVAL	[ ]	TECHNICAL ASSISTANCE	[ ]

NO ENTRIES FOR ITEMS 12, 13, AND 14.

15. PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1955

1. D. Burk and G. Hobby, Rapid and Sensitive Electrochemical and Hydraulo-manometric Measurements of Chemosynthetic Oxygen Exchange in Thermophils. Fed. Proc., 14, 187 (1955).

2. D. Burk, G. Hobby, and J. Hunter, Quantum Efficiencies of Photosynthesis and Cell Growth in Thermophilic Chlorella at High Light Intensities. Science, 121, 620 (1955).

3. D. Burk, G. Hobby, and J. Hunter, The Influence of Assimilatory Quotient, Cell Anabolism, and Growth on Photosynthetic Quantum Efficiency. Fed. Proc., in press.

16. HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1955

None

PROJECT REPORT FORM

1. NCI (INSTITUTE) 2. Laboratory of Biochemistry (LABORATORY OR BRANCH)

3. Cytochemistry (SECTION OR SERVICE) 4. -------- (LOCATION (IF OTHER THAN BETHESDA)) 5. NCI-330 (SERIAL NO)

Combined Actions of Anti-cancer Agents and Hormonal Systems that Inhibit Glucose Utilization in Cancer Metabolism and Growth
PROJECT TITLE

6. D. Burk and M. Woods
PRINCIPAL INVESTIGATOR(S)

7. J. Hunter
OTHER INVESTIGATORS

8. PROJECT DESCRIPTION

Objectives: To determine the action and mode of action of anti-cancer agents when used in vitro and in vivo in conjunction with relatively tumor-specific inhibitors of glucose utilization such as components of the hormonal anti-insulin complex.

Methods Employed: Tumor slices are either exposed in vitro to the compound under study, or the compound is administered in vivo and the effects on in vitro metabolism subsequently determined. Methods of metabolic analysis developed in connection with studies of insulin-anti-insulin hormonal systems are employed to evaluate quantitatively and qualitatively the effects and mechanism of action of the agent under test. A series of tumors exhibiting a spectrum of hormonal sensitivities are employed as test systems.

Major Findings: Certain podophyllin compounds, or newly prepared fractions of Podophyllum peltatum were found to inhibit in vitro the $Q^{N}2CO_2$ of S91 melanoma synergistically with either testosterone or diethylstilbestrol. When one of these fractions (CC7E) was tested in vivo (intraperitoneal in 10% polyvinylpyrrolidone (PVP) it was found that 5 to 10 gamma (per gram of body weight) caused little or no intratumoral necrosis. Likewise 100 gamma of diethylstilbestrol was completely non-inhibitory in vivo. However, when the two compounds were injected simultaneously at these dosages, very marked tumor destruction was apparent within 24 hours. Such combined injections were generally not strongly toxic to the mice although reversible splenic involution occurred. The latter, an evidence of systemic stress, was present in all cases where CC7E was used alone or in combination with steroid. It was absent, however, in mice treated with diethylstilbestrol only. CC7E given alone at concentrations of 20 gamma, or more,

per gram of body weight caused marked tumor necrosis. The data suggest that the tumor necrotizing properties of these podophyllin fractions and compounds may depend upon their in vivo potentiation of endogenous steroids of the stress-modifiable insulin:anti-insulin system which regulates the rate of the hexokinase reaction (glucose + ATP yields glucose-6-phosphate + ADP). The investigation of the possible use of podophyllin compounds in low concentrations as potentiators in steroid chemotherapy of other types of tumor is indicated.

A number of special problems are involved in attempting to translate, from in vitro to in vivo, the action of various potential chemotherapeutic agents on the metabolism of the cancer cell. Among others, these include the problem of tolerated in vivo dosages, excretion of the agent, detoxication of the agent by the host, and last but not least, the difficulty of distinguishing between tumor necrosis resulting from direct action of the drug in contrast to the indirect effects of toxic action on the tumor blood vessels. This latter, of course, may involve response of enzymic systems in the blood vessels themselves similar to those responding in the tumor cells in vitro. With these precautions in mind it was considered desirable to investigate certain model chemotherapeutic systems in vitro utilizing tissue slices, ascites tumors and/or, tissue cultures.

As reported many years ago by Warburg, it was found that cancer cells (S91, K-2) can survive in vitro at 38° C in the absence of oxygen for long periods (several days) if adequate glucose (0.1 t 0.2%) is present. On the other hand, if glucose is absent, the cells can survive only if oxygen is present. If both glucose and oxygen are absent the cells are rapidly destroyed. A model syste was established in which a specific inhibitor of glucose metabolism, acetylpodophyllotoxin-ω-pyridinium chloride (NCI-3022) was couple with a second agent, 2-4-dinitrophenol. The latter is capable of severely damaging both respiratory and glycolytic enzymes in the presence of glucose providing the first inhibitor (NCI-3022) is also present. In such a system oxygen plays an essential and synergistic role in producing irreversible cell injury. Since NCI-3022 inhibits only insulin-sensitive glycolysis, no appreciable synergistic effect with 2-4-dinitrophenol was obtained in the Krebs-2 carcinoma. However, when certain of the newly isolated alcohol-soluble fractions of podophyllum were substituted for the pure compound a considerable synergism with 2-4-dinitrophenol and oxygen was obtained in this strongly anti-insulin resistant tumor. Somewhat similar synergistic combinations were established with certain samples of penichromin, podophyllum derivatives and/or 2-4-dinitrophenol.

Significance to Cancer Research: The data show that the sensitivity to naturally occurring glucose metabolism-regulating hormones can be utilized to increase susceptibility of the cancer cell to simultaneously, or sequentially administered unnatural inhibitors of metabolism which may then act synergistically with oxygen to

PROJECT REPORT FORM (Cont'd)

0. NCI-330
SERIAL NO.

1.
BUDGET ACTIVITY:

RESEARCH	[x]	ADMINISTRATION	[ ]
REVIEW AND APPROVAL	[ ]	TECHNICAL ASSISTANCE	[ ]

0 ENTRIES FOR ITEMS 12, 13, AND 14.

5.
PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1955

1. M. Woods, J. Hunter, and D. Burk, Regulation of Glucose Utilization in Tumors by a Stress-modified Insulin:Anti-insulin System. J. Nat. Cancer Inst., 16, 351 (1955).

2. M. Woods, J. Hunter, and D. Burk, A Model of Multiple Chemotherapy: Synergistic Action of a Podophyllin Derivative, 2-4-Dinitrophenol, and Oxygen. Proc. Amer. Assn. Cancer Res., in press.

3. M. Woods, G. Hobby, and D. Burk, Synergistic Action between a Podophyllum Extract and Sex Steroids in Tumor Necrotization and Glycolysis. Proc. Amer. Assn. Cancer Res., in press.

4. M. Woods and D. Burk, Differential Metabolic and Necrotizing Responses of Tumors to Podophyllin and Colchinine Derivatives. Fed. Proc., in press.

5. D. Burk, J. Hunter, and W. H. Everhardy, On the Origin of Cancer Cells (Translation and Revision of Article by Otto Warburg), Science, in press.

6.
HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1955

None

No. 9 Continued. NCI-330

bring about irreversible damage to the malignant cell. In the absence of marked sensitivity to the hexokinase reaction-regulating hormones (e.g., testosterone, estradiol (or diethylstilbestrol)) considerable progress toward a synergistic type of inhibition was made with newly isolated alcohol-soluble fractions of Podophyllum peltatum.

Proposed Course of Project: Continuation of the same lines of attack is contemplated with particular emphasis on further isolation and utilization of active exogenous tumor-necrotizing factors (podophyllin fractions, penichromin fractions, etc.) including the natural anti-insulin lipoprotein of the anterior pituitary. In this connection certain clonal lines of tissue culture cells, possessing varying degrees of malignancy (Drs. Sanford and Earle) show promise as valuable test systems.

PROJECT REPORT FORM

1. NCI (INSTITUTE) 2. Laboratory of Biochemistry (LABORATORY OR BRANCH)

3. Cytochemistry (SECTION OR SERVICE) 4. ------- (LOCATION (IF OTHER THAN BETHESDA)) 5. NCI-331 (SERIAL NO)

6. Sub-cellular Localization of Insulin Action in Carbohydrate Metabolism and Tumor Growth (PROJECT TITLE)

7. P. Hochstein (Research Fellow) (PRINCIPAL INVESTIGATOR(S))

8. M. Woods and D. Burk (OTHER INVESTIGATORS)

9. PROJECT DESCRIPTION

Objectives: The objectives of this research are to study the sub-cellular mechanisms of insulin:anti-insulin regulation of carbohydrate metabolism and to relate these mechanisms to the growth of normal and malignant tissues in vivo.

Methods Employed: Cells of tumors which vary in the extent to which their glucose metabolism is sensitive to insulin are disrupted by mechanical means. The effects of insulin and insulin-opposers on the glycolysis of subcellular components are studied by manometric techniques.

Major Findings: It has been established (J. Nat. Cancer Inst., 16, 351, 1955) that insulin, anti-insulin hormones, and their potentiators play a key role in the regulation of glucose metabolism in tumor cells. It has also been shown that this control is mediated by the hexokinase reaction. In continuation of efforts toward a further understanding of the subcellular mechanisms by which this stress-modifiable system operates, a new type of evidence has been obtained that insulin plays a role in the subcellular glycolysis of certain tumors. Homogenates of S91 mouse melanoma prepared in sucrose, and fortified only with DPN, yielded nearly linear rates of anaerobic glycolysis ($Q^{N_2}CO_2$) for periods up to 60 minutes at 20° C., with glucose as substrate. However, homogenates prepared from aliquot tumor slices which had been preincubated in Krebs-Ringer solution with 0.2% glucose and 0.04 M bicarbonate, and centrifuged with or without washing, exhibited marked and progressive rates of decay in $Q^{N_2}CO_2$ values. It was demonstrated that preincubation resulted in an activation of ATPase as measured directly with added ATP in the absence of glucose. The decay in glycolytic rate with glucose in such homogenates could be prevented by the addition to the homogenate

of either ATP or ATPase restraining substances, or by the presence of oxygen which induces ATP formation. The addition of 0.2 units of crystalline low-zinc insulin/ml. to tumor slices during preincubation (though not afterward to the homogenate preparation) likewise reversed the decay in varying extent. Under the conditions reported here insulin appears to play a key role in maintaining the phosphorylating capacity of ATP-deficient subcellular glycolytic systems, presumably over the same hexokinase system as involved in intact cells and in types of subcellular preparations obtained without preincubation from temperature stressed animals.

Significance to Cancer Research: The metabolism and growth of tumors is geared to the utilization of glucose. An understanding of the mechanisms by which glucose metabolism is regulated is essential to the development of a rationale of chemotherapy and an understanding of the process of carcinogenesis.

Proposed Course of Project: It is proposed to continue these investigations to elucidate the interaction of insulin and anti-insulin hormones in regulating the phosphorylating capacity of subcellular, glucose utilizing systems of tumors. The action of anti-insulin potentiating substances on this regulatory mechanism will also be studied.

PROJECT REPORT FORM (Cont'd)

10. NCI-331
SERIAL NO.

11.
BUDGET ACTIVITY:

RESEARCH	[x]	ADMINISTRATION	[ ]
REVIEW AND APPROVAL	[ ]	TECHNICAL ASSISTANCE	[ ]

NO ENTRIES FOR ITEMS 12, 13, AND 14.

15.
PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1955

1. P. Hochstein, M. Woods, and D. Burk, Insulin-reversible, Stress-induced Inhibition of Cell Free Glycolysis in S91 Mouse Melanoma Homogenates. Fed. Proc., 14, 227 (1955).

2. P. Hochstein, On the Role of Insulin in Glycolyzing Tumor Homogenates. Proc. Am. Assn. Cancer Res., in press.

16.
HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1955

None

PROJECT REPORT FORM

1. NCI
INSTITUTE

2. Laboratory of Biochemistry
LABORATORY OR BRANCH

3. Cytochemistry
SECTION OR SERVICE

4. ---------
LOCATION (IF OTHER THAN BETHESDA)

5. NCI-332
SERIAL NO

6. Differential Effects of Temperature Stress on Growth of Transplanted Mouse Tumors
PROJECT TITLE

7. J. Hunter
PRINCIPAL INVESTIGATOR(S)

8. M. Woods and D. Burk
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objective: To determine the effect of temperature stress on the growth of transplanted tumors.

Methods Employed: Tumors are available which differ in their growth response to temperature stress and, similarly, in their sensitivity to temperature-induced, insulin-reversible lowering of glycolysis over host mechanisms and their glycolytic response to various podophyllum derivatives. Tissue from such varying tumors is inoculated into host animals and the growth of these tumors is determined by periodic caliper measurements in 3 dimensions. Growth and metabolic data from the various tumor types studied are analyzed.

Major Findings: A differential growth response was observed in the S91 melanoma and a high temperature induced partially amelanotic derivative of the S91 melanoma, S91(a), in strain DBA mice. Growth of the S91 melanoma was inhibited in mice kept at 33° C, but the inhibition was less than when the host animals were kept at 35° C. Exposure to an environmental temperature of 25° C reversed the inhibition. S91(a) tumors grow slower in animals kept at 35° C than in animals kept at 25° C but grew faster in animals kept at 33° C than in animals kept at 25° C. Maintenance of these tumor-bearing mice at an environmental temperature of 33° C, only 2° above the optimum environmental temperature, elicited a chronic stress response indicated in part by loss of body weight and splenic involution. These observations indicate that tumors of different origin, and even variant tumors of the same origin, react differently to endocrine changes in the host resulting from the stressing effects of high temperature. It is further indicated that the same level of

No. 9 Continued.

endocrine secretion may inhibit or stimulate tumor growth according to the genetic and metabolic character of the tumor involved.

Significance to Cancer Research: The problem of cancer control is to a great extent a problem of abnormal growth control. Any information regarding the ability of the host through physiological changes to control neoplastic growth or to lose such control is significant to cancer research.

Proposed Course of Research: More detailed studies of the sensitivity of various tumors to temperature induced variations of endocrine balance will be pursued.

PROJECT REPORT FORM (Cont'd)

10. NCI-332
SERIAL NO.

11.
BUDGET ACTIVITY:

RESEARCH	[x]	ADMINISTRATION	[ ]
REVIEW AND APPROVAL	[ ]	TECHNICAL ASSISTANCE	[ ]

NO ENTRIES FOR ITEMS 12, 13, AND 14.

15.
PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1955

1. J. Hunter, Differential Effects of Temperature on the Growth of Certain Transplanted Tumors in Strain DBA Mice. J. Nat. Cancer Inst., 16, 405 (1955).

2. M. Woods, J. Hunter, and D. Burk, Regulation of Glucose Utilization in Tumors by a Stress-modified Insulin:Anti-insulin System. J. Nat. Cancer Inst., 16, 351 (1955).

3. J. Hunter, Stress Induced Stimulation of Growth in a Derivative of the S91 Melanoma. Proc. Amer. Assn. Cancer Res., in press.

16.
HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1955

None

PROJECT REPORT FORM

1. NCI (INSTITUTE) 2. Laboratory of Biochemistry (LABORATORY OR BRANCH)

3. Cytochemistry (SECTION OR SERVICE) 4. ---------- (LOCATION (IF OTHER THAN BETHESDA)) 5. NCI-333 (SERIAL NO)

6. Steroidal Inhibitors in Oxidation and Glycolytic Enzyme Systems in Tumors (PROJECT TITLE)

7. K. Wight (PRINCIPAL INVESTIGATOR(S))

8. D. Burk (OTHER INVESTIGATORS)

9. PROJECT DESCRIPTION

Objectives and Methods Employed: Electrometric methods are combined with manometry and chemical analyses for the study of biochemical reactions such as change in oxygen, oxidation-reduction potential, carbon dioxide and pH.

Results: Diethylstilbestrol inhibited oxygen consumption, at low CO_2 pressure, of Krebs-2 ascites cells, tumor slices of Harding-Passey and S91 melanomas, S91A amelanotic melanoma, and C3HBA adenocarcinoma. Diethylstilbestrol also inhibited respiration and aerobic glycolysis simultaneously, with physiological CO_2 pressures (Summerson manometry), in Krebs-2 ascites cells and the following tissue slices: liver, brain, Harding-Passey and S91 melanomas.

Diethylstilbestrol inhibited the total aerobic and anaerobic acid production of a number of tissues at both the cellular and subcellular levels: liver, brain, C3HBA adenocarcinoma, Krebs-2 ascites and Harding-Passey and S91 melanomas. The respiratory quotient was usually raised as was also the percent Pasteur effect. Lactic acid production was inhibited by stilbestrol in the case of the S91 melanoma but unchanged in the case of brain. Inorganic phosphorus uptake by the S91 tumor was found to be inhibited both aerobically and anaerobically by diethylstilbestrol.

Studies with reduction of dyes as criteria of metabolic activity was performed. Liver mitochondrial suspensions in nitrogen partially reduced methylene blue and totally reduced brilliant cresyl blue in the presence of acetate, flavin adenine nucleotide, coenzyme A, DPN, and magnesium chloride; stilbestrol did not affect this reduction however.

PROJECT REPORT FORM (Cont'd)

10. NCI-333
SERIAL NO.

11.
BUDGET ACTIVITY:

RESEARCH	[x]	ADMINISTRATION	[ ]
REVIEW AND APPROVAL	[ ]	TECHNICAL ASSISTANCE	[ ]

NO ENTRIES FOR ITEMS 12, 13, 14, 15, AND 16.

PROJECT REPORT FORM

1. NCI — INSTITUTE
2. Laboratory of Biochemistry — LABORATORY OR BRANCH
3. Cytochemistry — SECTION OR SERVICE
4. --------- — LOCATION (IF OTHER THAN BETHESDA)
5. NCI-334 — SERIAL NO

6. The Occurrence and Function of a Stress-modifiable Insulin:Anti-insulin Hormonal Complex Regulating Glucose Utilization in Cancer Metabolism and Growth
PROJECT TITLE

7. M. Woods and D. Burk
PRINCIPAL INVESTIGATOR(S)

8. J. Hunter and P. Hochstein
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: To develop in vitro metabolic procedures for defining qualitatively and quantitatively the operation of a stress-modifiable insulin:anti-insulin hormonal mechanism that regulates cellular glucose utilization, and to determine its importance in controlling cancer metabolism and growth.

Methods Employed: Tumor-bearing mice are exposed to normal (20 to 25° C) or stressing (35 to 40° C) environmental temperatures, and the effects on tumor metabolism and growth determined. In vitro measurements of anaerobic glucose uptake and glycolysis (QN_2CO_2), in the presence and absence of insulin and certain steroids, are expressed as rate-time curves at successive cycles of temperatures of incubation (e.g., 20° to 40° to 20° to 40°, or 20° to 10° to 40°). Metabolic findings in vitro are correlated with in vivo effects of temperature stress on tumor survival and growth. Comparative metabolic studies with human tumors are made when feasible.

Major Findings: In pursuit of the objective to determine the importance of the stress-modifiable insulin:anti-insulin system that regulates glucose utilization, in possible control of cancer metabolism and growth, certain experiments involving potentiators of this system were undertaken. Since a podophyllotoxin derivative, acetyl podophyllotoxin-ω-pyridinium chloride (NCI-3022) has a sex-steroid-like action on glycolysis in insulin-sensitive tumors, but little or no action in relatively insensitive tumors such as the Krebs-2 carcinoma, the action of other related compounds or podophyllum fractions on these two tumors was undertaken. Compounds most active in inhibiting glycolysis of S91 melanoma were podophyllotoxin, alpha peltatin, and beta peltatin. Quercetin was

intermediate in activity while iso-podophyllic acid and podophyllotoxin glucoside were essentially inactive. The ability to inhibit insulin-sensitive glycolysis thus roughly parallels the capacity to necrotize in vivo as found by Leiter, Waravdekar, et al. The Krebs-2 carcinoma was insensitive to all of the pure podophyllin derivatives except quercetin in high concentrations. However, certain alcohol-soluble fractions of commercial podophyllin, or of fresh tissues of Podophyllum peltatum, L. were obtained which inhibit glycolysis of both S91 and Krebs-2 tumors. Certain of these (e.g., CC7E) at low concentrations (3 to 30 p.p.m.) selectively inhibit insulin-sensitive glycolysis in vitro (e.g. in melanoma and spontaneous mammary carcinoma) and, are 3 to 10 times as active as any of the pure compounds (or mixtures thereof) derived from podophyllin. In contrast to the podophyllins, the colchicines tested, were weak inhibitors of glycolysis, and no significant correlations between in vitro and in vivo (necrotization) could be found.

Dr. George Wolff of the Genetics Section, who collaborated with the Cytochemistry Section during the year along the lines of the present project, obtained further evidence that the obesity gene (ob) influences the insulin:anti-insulin regulation of glucose metabolism in Harding-Passey tumors implanted in mice of the ob genotype. Clear cut evidence for the direct action of exogenous insulin in kidney in vitro glycolysis also resulted from these studies. Dr. Wolff's detailed results are reported in a separate project (serial No. NCI-426).

Dr. Hochstein's work with sub-cellular preparations of S91 melanoma has demonstrated that the insulin:anti-insulin regulation of glucose metabolism proceeds at the level of the hexokinase reaction. His studies promise to go far in elucidating the actual mechanisms involved in the operation of this system. These results are reported separately (serial No. NCI-331).

Significance to Cancer Research: A variety of compounds have been found which selectively inhibit glycolysis by potentiating the hormonal system which, in opposition to insulin, restrains the hexokinase reaction. Technics of metabolic analysis, utilizing these compounds have been developed which allow a rapid metabolic characterization of tumors with respect to their sensitivity to sex steroids and insulin. These metabolic tools should prove useful in determining degrees of malignancy and in developing chemotherapeutic procedures involving steroid hormone.

The finding of Dr. Wolff that gonadectomy in normal and ob mice results in sex-linked alterations in the anti-insulin regulation of tumor glycolysis is of particular significance because it provides a new type of evidence for the in vivo functioning of sex steroids in the regulation of glucose metabolism.

Dr. Hochstein's findings (serial No. NCI-331) aid very considerably in an understanding of the biochemical basis for the malignant

PROJECT REPORT FORM (Cont'd)

0. NCI-334
SERIAL NO.

1. BUDGET ACTIVITY:

RESEARCH	[x]	ADMINISTRATION	[ ]
REVIEW AND APPROVAL	[ ]	TECHNICAL ASSISTANCE	[ ]

2. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 OR 1957:

Dr. George Wolff, NCI Research Fellow in the Genetics Section of the Laboratory of Biology, has been conducting metabolic and biochemical studies in cooperation with the cytochemistry section during 1955.

0 ENTRIES FOR ITEMS 13 AND 14.

5. PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1955

1. M. Woods, J. Hunter, and D. Burk, Regulation of Glucose Utilization in Tumors by a Stress-modified Insulin:Anti-insulin System. J. Nat. Cancer Inst., 16, 351 (1955).

2. J. Hunter, Differential Effects of Temperature on the Growth of Certain Transplanted Tumors in Strain DBA Mice. J. Nat. Cancer Inst., 16, 405 (1955).

3. M. Woods and D. Burk, Podophyllotoxin Derivative as Inhibitor of Insulin-sensitive Tumor Glycolysis. Proc. Amer. Assoc. Cancer Res., 2, 54 (1955).

4. P. Hochstein, M. Woods, and D. Burk, Insulin-reversible Stress-induced Inhibition of Cell-free Glycolysis in S91 Mouse Melanoma Homogenates. Fed. Proc., 14, 227 (1955).

5. G. L. Wolff, Effects of the ob Gene, Age, and Sex on the Anaerobic Glycolysis of Mouse Kidney and Melanoma. Proc. Amer. Assn. Cancer Res., 2, 54 (1955).

6. D. Burk and M. Woods, On the Metabolism of the Cancer Cell. Proc. Amer. Assn. Cancer Res., in press.

transformation of cells and are suggestive with respect to problems of chemotherapy.

The new S91 tumor line developed by Mr. Hunter should prove to be a valuable cancer research tool becuase of the possibilities for its use in determining the critical relationships between hereditary (in the sense of tumor cell reproduction) sensitivity to hormones of the insulin:anti-insulin system and the levels of these hormones required to give either anabolic or catabolic effects.

Proposed Course of Project: Continuation of the same lines of attack is contemplated with special emphasis on chemotherapeutic applications of the metabolic findings. It is planned to give special emphasis to the isolation and utilization of the anti-insulin lipoprotein fraction of the anterior pituitary.

o. 15 Continued. NCI-334

7. On the Origin of Cancer Cells by Otto Warburg (translated and revised by D. Burk, et al.), Science, in press.

8. J. Hunter, Stress Induced Stimulation of Growth in a Derivative of the S91 Melanoma. Proc. Amer. Assn. Cancer Res., in press.

9. P. Hochstein, On the Role of Insulin in Glycolyzing Tumor Homogenates. Proc. Amer. Assn. Cancer Res., in press.

6. HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1955

None

PROJECT REPORT FORM

1. NCI — INSTITUTE
2. Laboratory of Biochemistry — LABORATORY OR BRANCH
3. Protein Chemistry — SECTION OR SERVICE
4. --------- — LOCATION (IF OTHER THAN BETHESDA)
5. NCI-335 — SERIAL NO

6. Nutrition
PROJECT TITLE

7. Winitz, Birnbaum, Greenstein and Greenstein (Collaborating Pediatrician)
PRINCIPAL INVESTIGATOR(S)

8. Brooks
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: To prepare a completely water soluble diet composed of optically pure amino acids, crystalline vitamins, minerals, carbohydrate, and fats with the double objective of: A. Furnishing a complete nutritious mixture suitable for parenteral feeding of premature infants, postoperative patients and patients with gastro-intestinal inadequacies, and B. Studying the effect of controlled variation of the diet on normal growth, tumor growth and tumor/host relationships.

Methods: A diet was prepared based on known and estimated requirements for amino acids, vitamins, calories, and minerals. These essentials were supplied in soluble form in a diet complete with the exception of the essential fat requirements and the fat soluble vitamins. The former was then fed weanling rats by means of calibrated drinking tubes while the latter was supplied thrice weekly in supplement dishes. The growth curves, reproductive and lactating capacity of animals on this diet is then compared with animals on prepared Lab. chow.

For feeding in the solid form the diet is modified by blending in the fatty components and by substituting a standard complete salt mixture for the soluble salts.

In tumor studies the animals are placed on the complete synthetic diet for one week, implanted with tumor tissue and maintained for another week on the complete diet. After this period the animals are regrouped and subjected to the controlled modified diets.

Major findings: A group of 10 weanling male rats was raised to maturity on a 50% solution of the diet. Over a two-month period the animals gained about 200g on the diet. No symptoms of any deficiency or unnatural behavior were observed. A second group of male and female weanlings was started on the

diet and similar results are being obtained.

Ground laboratory chow fed to a small group of males over a similar period actually resulted in less growth.

Significance to cancer research: The availability of a soluble synthetic diet as described is a tool of unlimited value to the field of cancer research.

The amino acid portion of previously prepared synthetic diets has been composed for the most part of racemic derivatives, the D forms of which exert a variable and little understood overall effect on the metabolism of the animal. The elimination of all of these unnatural isomers from the diet allows a clear cut interpretation of the results of nutritional studies.

The elimination of one or more essential substances from the diet often causes in addition to its specific result greatly decreased intake resulting in the superimposed effect of general malnutrition to complicate the picture. The availability of a soluble easily forcefed mixture obviates this difficulty.

Healing and the general welfare of patients following radical surgery may be greatly promoted by the administration of a complete diet intravenously rather than the crude amino acid plus glucose mixtures customarily employed. In addition this will be a means of prolonging the life span of patients with severe gastro-intestinal cancer.

Proposed course of project: As indicated, the reproductive and lactating capabilities of rats raised on the soluble diet will be studied. The results of these investigations should indicate the completeness and efficiency of the diet from all possible approaches.

Plans are underway for an investigation of the suitability of this mixture for the parenteral feeding of hopelessly premature, 1-2 lb., infants. The first approach will be in the nature of a careful study of the ability of more advanced prematures to assimilate the diet when administered per os. If satisfactory reactions are observed the diet will b administered by umbilical vein to the smaller infants.

The effect on tumor growth and tumor/host relationships of imbalance, or deficiency of amino acid intake will be studied by modifying the present diet in a specific and controlled manner.

Attempts to simplify and perfect the diet will continue.

PROJECT REPORT FORM (CONT'D)

0. NCI-335

SERIAL NO.

1. _____

BUDGET ACTIVITY:

RESEARCH	☒	ADMINISTRATION	☐
REVIEW AND APPROVAL	☐	TECHNICAL ASSISTANCE	☐

0 ENTRIES FOR 12, 13, AND 14.

5. _____

PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1955

None

6. _____

HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1955.

None

PROJECT REPORT FORM

1. NCI — INSTITUTE
2. Laboratory of Biochemistry — LABORATORY OR BRANCH
3. Protein Chemistry — SECTION OR SERVICE
4. -------- — LOCATION (IF OTHER THAN BETHESDA)
5. NCI-336 — SERIAL NO.

6. Studies on the Metabolism of Amino Acids and Related Compounds in Vivo
PROJECT TITLE

7. Greenstein, Gullino(Visiting Scientist), Winitz, Birnbaum, du Ruisseau (Visiting Scientist)
PRINCIPAL INVESTIGATOR(S)

8. Otey, B. B. Smith, R. Brooks, F. Hull, B. Whitaker
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

The objectives of this project is essentially to ascertain those enzyme levels at rates in vivo which are concerned in the basic metabolism of proteins and amino acids.

Each of the L- and D-forms of the 10 essential amino acids were administered singly by intraperitoneal injection to a large number of rats, and the LD_{50} levels determined by statistical computation. These amino acids were isoleucine, valine, leucine, phenylalanine, methionine, threonine, histidine, lysine, arginine, and tryptophan. The toxicity of these amino acids increased in the order given. In all cases the D-isomers were equally or less toxic than the corresponding L-amino acids.

The L-amino acids were given at $LD_{99.99}$ levels and blood sugars measured. After administration in every case there was a large or small hyperglycemia, but at death, isoleucine, valine, leucine, phenylalanine, methionine, and tryptophan caused a severe hypoglycemia, lysine a marked hyperglycemia, arginine a mild hyperglycemia, histidine a mild hyperglycemia, and threonine no change in the blood sugar level at all.

Mixtures of the 10 L-amino acids possessed a toxicity which was less than that calculated from the arithmetic mean of their individual toxicities. One compound of this mixture was removed at a time and the toxicity of the mixtures of 9 amino acids compared. In only 1 case was there good agreement between calculated and found toxicity, and that was in the mixture in which arginine was lacking. It appeared therefore that arginine exerted some sort of protective effect against the toxicity of the other amino acids. This was proven by adding L-arginine in varying amounts to an $LD_{99.9}$ mixture of the other 9 amino acids, and achieving at 2mM level a survival of 76% instead of a 100% mortality.

No. 9 cont'd. NCI-336

In order to see whether ammonia toxicity was involved in this picture, the LD_{50} level for ammonium acetate was determined with rats. At $LD_{99.9}$ levels of this compound, L-arginine given simultaneously protected 50% of the animals from death, but when given 1 hour before the ammonium acetate was given, 100% of the animals were protected. L-Ornithine, L-citrulline, D-arginine, ketoarginine, and α-acetyl-L-ornithine also protected to a greater or lesser degree. A large number of compounds related to arginine, however, were not protected. Those compounds which protected converted the ammonia to urea.

PROJECT REPORT FORM (CONT'D)

1. NCI-336

SERIAL NO.

1. _____

BUDGET ACTIVITY:

RESEARCH	/x/	ADMINISTRATION	/_/
REVIEW AND APPROVAL	/_/	TECHNICAL ASSISTANCE	/_/

) ENTRIES FOR ITEMS 12, 13, AND 14.

5. _____

PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1955

1. Gullino, Winitz, Birnbaum, Cornfield, Otey, and Greenstein. The Toxicity of Individual Essential Amino Acids and their Diastereomers in Rats and the Effect on Blood Sugar Levels. Archiv. Biochem. and Biophys. 58, 253 (1955).

2. Gullino, Winitz, Birnbaum, Otey, Cornfield, and Greenstein. The Toxicity of Essential Amino Acid Mixtures with Special Reference to the Protective Effect of L-Arginine. Archiv. Biochem. and Biophys. 58, 255 (1955).

3. Greenstein, Winitz, Gullino, and Birnbaum. Archiv. Biochem. and Biophys. 59, 302 (1955).

6. _____

HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1955.

None

PROJECT REPORT FORM

1. NCI
INSTITUTE

2. Laboratory of Biochemistry
LABORATORY OR BRANCH

3. Protein Chemistry
SECTION OR SERVICE

4. ---------
LOCATION (IF OTHER THAN BETHESDA)

5. NCI-337
SERIAL NO.

Amino Acid Syntheses
PROJECT TITLE

M. Winitz and R. Wade (Visiting Scientist)
PRINCIPAL INVESTIGATOR (S)

A. Kerr, H. Foster, G. Stewart
OTHER INVESTIGATORS

PROJECT DESCRIPTION

Objective: To develop new and simpler methods for the synthesis of amino acids.

Methods Employed: Techniques of organic chemistry - condensation reactions, fractionations, chromatography, etc.

Major Findings: A new and simple method for the synthesis of isoleucine and hydroxyproline has been developed.

Significance to Cancer Research: Amino acids are used extensively in this laboratory for nutrition and toxicity studies with both normal and tumor bearing animals. Their ready and economical availability thereby becomes a matter of some concern.

Proposed Course of Project: To develop new syntheses for the relatively rare diaminopimelic, α-aminopimelic and β-hydroxyglutamic acids.

PROJECT REPORT FORM

10. NCI-337
SERIAL NO.

11.
BUDGET ACTIVITY:

RESEARCH [x] ADMINISTRATION [ ]

REVIEW AND APPROVAL [ ] TECHNICAL ASSISTANCE [ ]

NO ENTRIES FOR ITEMS 12, 13, and 14.

15.
PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1955.

None

16.
HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1955.

None

PROJECT REPORT FORM

1. NCI — INSTITUTE
2. Laboratory of Biochemistry — LABORATORY OR BRANCH
3. Protein Chemistry — SECTION OR SERVICE
4. ---- — LOCATION (IF OTHER THAN BETHESDA)
5. NCI-338 — SERIAL NO.

6. The interaction of Co^{++} ions with acylase I
PROJECT TITLE

7. Marshall, (~~Visiting Scientist~~) Birnbaum, Greenstein
PRINCIPAL INVESTIGATOR(S)

8. none
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: To further our knowledge of the basic nature of Acylase I with a view toward making this preparation of even greater practical value in the general resolution procedures for racemic amino acids and toward gaining further insight into the fundamental interactions of active proteins with metals.

Methods employed: Optically pure acyl amino acids are incubated with the enzyme in the presence of varied amounts of cobalt acetate and the effect on the rates of hydrolysis are noted. The enzyme preparation is treated with cobalt under varying conditions and the effect on its activity is determined.

Major findings: 1) Many of the more resistant acylamino acids are more actively hydrolyzed in the presence of Co^{++} ions. 2) This finding has been employed to economical advantage in the resolution of acetyl-DL-isoleucine and other amino acids. 3) A new form of acylase (IA) more active against certain substrates has been prepared by incubating the standard preparation with cobalt acetate and dialyzing away the unbound metal. This to the authors knowledge is the first time the relative specificity of an enzyme has been altered by chemical means.

Significance to Cancer Research: The perfection of this enzyme as a reagent for the preparation of optically active amino acids makes even more easily available the large amounts of these isomers employed in metabolic, nutritional and other cancer studies. In addition any knowledge of the fundamental nature of enzyme action contributes to the understanding of normal or tumor growth and may suggest new approaches to the study of the cancer problem at large.

No. 9 cont'd. NCI-338

Proposed course of research: Further practical studies on the application of these findings to the resolution procedure are in progress. The nature of the metal-protein interaction in the absence of substrate is to be further investigated.

PROJECT REPORT FORM (CONT'D)

1. NCI-338

SERIAL NO.

1. _____

BUDGET ACTIVITY:

RESEARCH	[X]	ADMINISTRATION	[ ]
REVIEW AND APPROVAL	[ ]	TECHNICAL ASSISTANCE	[ ]

) ENTRIES FOR 12, 13, AND 14.

5. _____

PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1955

None

6. _____

HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1955.

None

PROJECT REPORT FORM

1. NCI
INSTITUTE

2. Laboratory of Biochemistry
LABORATORY OR BRANCH

3. Protein Chemistry
SECTION OR SERVICE

4. --------
LOCATION (IF OTHER THAN BETHESDA)

5. NCI-339
SERIAL NO

6. Purification, Physical Chemical Characterization, and Homogeneity of Proteins of Special Biochemical or Biophysical Significance.
PROJECT TITLE

7. E. A. Peterson and H. A. Sober
PRINCIPAL INVESTIGATOR(S)

8. F. J. Gutter, M. M. Wyckoff, M. E. Maver
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: To prepare and examine by a variety of techniques purified proteins with the view of gaining insight into the relationship between the gross architecture and microstructure of the macromolecule and its specific, unique, biological property.

Methods Employed: Chromatographically purified fractions are examined by physical chemical methods (such as sedimentation, diffusion, electrophoresis, spectrophotometry), by specific biological activity determinations (such as catalytic activity, substrate specificity, immunochemical reactivity, etc.) and by chemical methods (such as end group determinations, sequence studies, cross linkages etc).

Major findings: Hemoglobin has been studied and evidence for its heterogeneity has been adduced. It has been shown that a combination of urea and mercaptoethanol has a greater effect on the dissociation of the molecule into lower molecular weights than does either reagent alone and that human hemoglobin, in contrast to horse hemoglobin, is not dissociated by urea but exhibits a marked change in shape. A paper entitled "The Effect of Mercaptoethanol and Urea on the Molecular Weight of Hemoglobin" by F. J. Gutter, H. A. Sober, and E. A. Peterson has been submitted to the Archives of Biochemistry and Biophysics for publication.

Enzymes from spleen, heart, kidney etc. have been purified with good recovery of catalytic activity. New enzyme activities and substrate specificities have been encountered.

Proteins such as human albumin. and γ-globulin. have been shown by chromatographic examination to consist of several components. These components have exhibited differences when examined by the above techniques.

No. 9 cont'd. NCI-339

Significance to Cancer Research: It is assumed that a specific property or function of a biologically important macromolecule is related to its gross structure or chemical composition. Minor changes in the molecule, while sufficient to cause major biological disturbance have rarely been detected by conventional techniques. This has been the result of the inhomogeneity of the material studied, the application of the wrong criterion or the lack of sensitivity of the methods employed. Criteria of purity would seem to be one of the major prerequisites for the advancement of the knowledge of the relation of function to structure and composition.

Proposed course of project: Purification of hemoglobin components and examination of the different types of bonds maintaining the configuration of the hemoglobin molecule will be continued. Purification of the nucleases from spleen and the several acylases of kidney will be attempted. Large scale preparation and purification of the components of "Albumin" and "Y-globulin". siderophilin, and ceruloplasmin in purified form will be carried out.

PROJECT REPORT FORM (CONT'D)

1. NCI-339

SERIAL NO.

1. _____

BUDGET ACTIVITY:

RESEARCH	[x]	ADMINISTRATION	[ ]
REVIEW AND APPROVAL	[ ]	TECHNICAL ASSISTANCE	[ ]

) ENTRIES FOR 12, 13. AND 14.

5. _____

PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1955

None

6. _____

HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1955.

None

PROJECT REPORT FORM

1. NCI — INSTITUTE
2. Laboratory of Biochemistry — LABORATORY OR BRANCH
3. Protein Chemistry — SECTION OR SERVICE
4. -------- — LOCATION (IF OTHER THAN BETHESDA)
5. NCI-340 — SERIAL NO

6. Immunochemical Characterization of Protein Components of Serum — PROJECT TITLE

7. J. Oudin (Visiting Scientist) — PRINCIPAL INVESTIGATOR(S)

8. H. A. Sober, E. A. Peterson — OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: To set up and apply procedures for the immunochemical characterization and identification of chromatographically resolved protein components of serum.

Methods Employed: The very sensitive and specific agar-gel diffusion technique of Oudin, using 18 different and singly-reacting antibody preparations.

Major Findings: The procedures and apparatus for the examination of the chromatographically-obtained serum fractions have been instituted. In the very short time this project has been operating, it has been established that γ-globulin prepared chromatographically is immunochemically "purer" than that obtained by extensive salt fractionation, that some immunochemical components are only found in one fraction, and that many components have several immunochemical reactivities.

Significiance to Cancer Research: It is known that "pure" proteins contain several detectable immunochemical properties and that conversely, different proteins may contain the same immunochemical specificity. Immunochemical examination, in many instances provides the most sensitive method for the detection of contaminating proteins and alterations of structure and organization. Since proteins are key substances in the body and play a part in all activities of living matter, and since it is probable that a reflection of the disease process does exist among the proteins of the body, sensitive and specific methods must be available and applied to the study of the protein components of systems derived from normal and pathological conditions.

Proposed Course of Project: To examine and characterize immunochemically the chromatographically isolated fractions of serum and to use the immunochemical technique for the detection of contamination, inhomogeneity, or non-specificity of the isolated proteins.

PROJECT REPORT FORM (CONT'D)

10. NCI-340

SERIAL NO.

11.

BUDGET ACTIVITY:

RESEARCH	[x]	ADMINISTRATION	[ ]
REVIEW AND APPROVAL	[ ]	TECHNICAL ASSISTANCE	[ ]

NO ENTRIES FOR 12, 13, and 14.

15.

PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1955

None

16.

HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1955.

None

PROJECT REPORT FORM

1. NCI — 2. Laboratory of Biochemistry
INSTITUTE — LABORATORY OR BRANCH

3. Enzymes and Metabolism — 4. - - - - - — 5. NCI-341
SECTION OR SERVICE — LOCATION (IF OTHER THAN BETHESDA) — SERIAL NO.

6. Studies on the rapid destruction of erythrocytes in tumor-bearing animals.
PROJECT TITLE

7. Dr. Vincent E. Price and Dr. Robert E. Greenfield
PRINCIPAL INVESTIGATOR(S)

8. Mr. Wm. R. Sterling
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: To determine the mechanism by which red blood cells are rapidly lost from the circulation of tumor-bearing animals and to learn the fate of the destroyed cells.

Methods Employed: Erythrocytes of inbred strains of rats are labelled with Fe^{59} and injected into the bl od stream of rats bearing transplantable tumors. The disappearance of labelled cells from the circulation is followed by determining the radioactivity of 20 microliter samples of blood which are obtained from the tail. Shortly before sacrifice the circulating blood is labelled by injection of chromium-51 labelled cells. The distribution of radioiron within the tumor and host tissues is then examined. Determination of the concentration of radiochromium within each tissue by a differential counting technique serves as a measure of the circulating blood remaining within each tissue and permits measurement of the noncirculating radioiron remaining in each tissue.

Major Findings: 1) In rats with tumors of 10 percent of the body weight the iron pool in the tumor was larger than the iron pool in the liver, which is the major iron storage organ of the body. 2) In rats with tumors weighing 10 to 20 percent of the body weight labelled erythrocytes disappeared from the circulation with a half life of 3 to 7 days, depending on the size and location of the tumor. 3) A large portion of the radioiron which disappeared from the blood stream was recovered in the tumor. 4) When the hemoglobin of red cells was labelled with chromium-51 most of the radiochromium labelled hemoglobin which disappeared from the blood stream was recovered in the tumor. 5) When chromium-labelled erythrocytes were lyzed and injected very slowly by intravenous infusion almost none of the radiochromium-labelled hemoglobin was recovered in the tumor. Most of the radioactivity was found in the liver and in the urine. This is considered strong evidence that the chromium-labelled hemoglobin entered the tumor in intact red cells. If a hemolytic process had occurred in these tumor-bearing animals which

released hemoglobin into the circulating blood the radiochromium would have been found in the liver and urine instead of in the tumor.

Significance to Cancer Research: Several clinical papers have recently suggested that the decreased red cell survival time found in cancer patients was due to a hemolytic process brought about by release from the tumor of a hemolytic factor into the blood stream. If such a hemolytic factor did occur it might be of great value as a diagnostic tool and its characterization would be important in advancing our understanding of tumor metabolism. As yet no evidence for such a circulating hemolytic factor has been found in our tumor-bearing animals.

Proposed Course of Project: 1) Studies are being carried out to study the fate of hemoglobin iron, porphynin, and protein within the tumor and the extent to which they are utilized in tumor metabolism. 2) Studies are being contemplated with Dr. Jessie Steinfeldt of the General Medicine Branch to study the fate of erythrocytes in cancer patients and to learn the extent in which the findings described above in tumor-bearing animals are also found in human patients.

PROJECT REPORT FORM (CONT'D)

10. NCI-341

SERIAL NO.

11.

BUDGET ACTIVITY

RESEARCH	[x]	ADMINISTRATION	[ ]
REVIEW AND APPROVAL	[ ]	TECHNICAL ASSISTANCE	[ ]

NO ENTRIES FOR ITEM 12.

13.

IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH.

Dr. Jesse Steinfeldt of the General Medicine Branch is studying the decreased red cell survival time of cancer patients. A contemplated joint study on the fate of erythrocytes in these patients has been mentioned above.

NO ENTRIES FOR ITEM 14. 15, AND 16.

PROJECT REPORT FORM

1. NCI — 2. Laboratory of Biochemistry
INSTITUTE — LABORATORY OR BRANCH

3. Enzymes and Metabolism — 4. - ------- — 5. NCI-342
SECTION OR SERVICE — LOCATION (IF OTHER THAN BETHESDA) — SERIAL NO.

6. Studies on the anemias of tumor-bearing animals.
PROJECT TITLE

7. Drs. Robert E. Greenfield and Vincent E. Price
PRINCIPAL INVESTIGATOR(S)

8. Mr. Wm. R. Sterling
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION:

Objectives: To study the iron, porphyrin, and protein metabolism of tumor-bearing animals in order to evaluate the various factors contributing to their anemia.

Methods Employed: 1) Measurement of plasma transferrin, plasma iron, and erythrocyte porphyrin levels in various states of anemia and therapy. 2) Radioisotopic techniques using radioiron; isotopically-labelled transferrin, the iron-transport protein of the plasma; and isotopically labellederythrocytes in which the hemoglobin is labelled with C^{14}, Cr^{51}, or both.

Major Findings: 1) Studies on the rate at which radioiron is cleared from the plasma of normal and tumor-bearing rats and incorporated into erythrocytes indicate that red cells are synthesized at a very rapid rate in these tumor-bearing animals. 2) When plasma labelled with radioiron is injected into tumor-bearing rats a considerable fraction is found in the tumor at short time intervals following the injection. This fraction is considerably more than would be expected have entered the tumor by the labelling of red cells and thi r passage into the tumor in these short time intervals. This suggests that iron may enter the tumor directly from the plasma.

Significance to Cancer Research: Advanced cancer states are frequently accompanied by a severe anemia. Little is known about the anemia which accompanies malignancy. In the past it has usually been classed along with the anemia of infection, among the chronic anemias in which there is a deficiency of iron utilization for red cell production. The results obtained on our tumor-bearing rats indicate a very rapid rate of red cell production. Because of the importance of anemia in the advanced cancer state a thorough study of the various factors which may enter into its etiology.is indicated.

No. 9 cont'd. NCI-342

Proposed Course of Research: 1) To measure the rate at which radioiron enters the tumor directly from the plasma. 2) To determine if isotopically labelled transferrin enters the tumor with the radioiron, and, if so, to determine whether it is directly utilized for tumor growth. 3) To determine the effect of nutrition and iron therapy on the anemia of tumor-bearing rats. 4) To determine the free erythrocyte coproporphyrin of normal and tumor-bearing rats. This is considered to be a sensitive index of the rate of hemoglobin synthesis. 5) To determine the free erthrocyte protoporphyrin in tumor-bearing rats. Erythrocyte protoposphyrin accumulates in iron deficiency states. 6) To determine the fate of the large pool of iron in tumors during tumor therapy, and whether iron toxicity occurs if large amounts of iron are rapidly released into the circulation during therapy.

PROJECT REPORT FORM (CONT'D)

0. NCI-342

SERIAL NO.

1. _____

BUDGET ACTIVITY:

RESEARCH	X	ADMINISTRATION	
REVIEW AND APPROVAL		TECHNICAL ASSISTANCE	

0 ENTRIES FOR ITEMS 12, 13, 14, 15 AND 16.

PROJECT REPORT FORM

1. NCI 2. Laboratory of Biochemistry
INSTITUTE LABORATORY OR BRANCH

3. Enzymes and Metabolism 4. - - - - - - - 5. NCI-343
SECTION OR SERVICE LOCATION (IF OTHER THAN BETHESDA) SERIAL NO.

6. Hormonal Factors in Acetylaminofluorene Carcinogenesis
PROJECT TITLE

7. James B. Gilbert
PRINCIPAL INVESTIGATOR(S)

8. Project in collaboration with Dr. Harold P. Morris and Dr. John Weisburger (Nutrition and Carcinogenesis section)
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: These are several, all related to the effect of thyroidectomy in preventing development of hepatomas in the rat administered the carcinogen(s) 2-acetylaminofluorene or 2-diacetylaminofluorene (e.g. vide Morris and Firminger J.N.C.I. Feb. 1956. Bielschowsky and Hall Brit. Journ. Cancer 7. 358 (1953)): a) to study qualitatively (and quantitatively)the urinary metabolites of 2-acetylaminofluorene (AAF) in the thyroidectomized animal and compare these results with the excretion products obtained in the normal animal administered AAF. b) to study the differences in protein binding of AAF in livers of thyroidectomized rats as compared with liver protein from intact rats. c) to establish if thyroid extract or thyroxine is sufficient to allow development of hepatomas in the AAF-treated, thyroidectomized rat.

Methods Employed: The rats to be used in these experiments are AxC male rats (high susceptability to liver tumors). The 2-AAF used is carbon-14 labeled in the 9 position and the usual techniques of column and paper chromatography, radioautography, carrier isolation procedures etc. will be employed in identification of urinary metabolites. Protein binding studies involves specific activity determinations after repeated precipitations.

Major Findings: a) Considerable progress was made by Drs. Morris and Weisburger whose annual reports should be consulted for specificities. This investigator is new to this program. b) Under a previous program the finding that threonine is synthesized by a rat liver enzyme from acetaldehyde and glycine has been elucidated.

Significance to Cancer Research: The protective effect of thyroidectomy, against development of liver tumors, is an interesting approach to the general problem of the hormonal factors in the etiology of cancer. Possible

No. 9 cont'd. NCI-343

qualitative etc. differences in metabolites. protein binding etc., with and without thyroid present, could go far in elucidating the problem of carcinogenesis.

Proposed Course of Project: It is planned to study the urinary metabolites first, the protein binding work, secondly; and the effect of thyroid extract, last or if possible, concomitantly.

PROJECT REPORT FORM CONT'D

5. NCI-343

SERIAL NO.

11.

BUDGET ACTIVITY:

RESEARCH	[x]	ADMINISTRATION	[ ]
REVIEW AND APPROVAL	[ ]	TECHNICAL ASSISTANCE	[ ]

D ENTRIES FOR ITEMS 12, 13, AND 14.

5.

PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1955.

Publications from another project:

(1) John Z. Hearon and James B. Gilbert. New Methods for the Calculation of Association Constants of Complex Ion Systems. J. Am. Chem. Soc. 77, 2594 (1955).

(2) James B. Gilbert, M. Clyde Otey and John Z. Hearon. Association Constants of Cobalt-glycine and Cobalt-glycylglycine Complexes in Aqueous Solution. J. Am. Chem. Soc. 77, 2599 (1955).

6.

HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1955.

None

PROJECT REPORT FORM

1. NCI 2. Laboratory of Biochemistry
INSTITUTE LABORATORY OR BRANCH

3. Nutrition and Carcinogenesis 4. ---------- 5. NCI-344
SECTION OR SERVICE LOCATION(IF OTHER THAN BETHESDA) SERIAL No.

6. Sex and sex-hormonal factors involved in the mechanism of carcinogenesis
PROJECT TITLE

7. Harold P. Morris
PRINCIPAL INVESTIGATOR(S)

8. Harlan I. Firminger and Billie P. Wagner
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objective: A study of the influence of sex and sex hormonal factors involved in the induction of cancer of the liver by 2-diacetylaminofluorene

Methods Employed. Male, female, castrated male, castrated male + diethylstilbestrol, castrated female, and castrated female + testosterone proprinate AxC strain rats were fed a diet containing .05% of the carcinogenic chemical 2-diacetylaminofluorene under various conditions. The onset of morphological liver lesions and hepatomas was studied.

Major Findings: Morphological lesions interpreted as early hepatomas of the liver developed after 5 to 6 weeks of continuous feeding of the carcinogen. These lesions developed mostly in the intact males and castrated females receiving testosterone proprinate. Intact females, castrated females, and castrated males treated with diethylstilbestrol were more resistant. Reducing the rate of carcinogen intake through intermitent feeding of the carcinogenic diet delayed the appearance of hepatomas in the susceptible animals and in some cases lowered the incidence of hepatomas.

Lesions short of hepatomas were characterized histogically by proliferation of small bile ducts and portal cirrhosis, associated with areas of hepatic-cell hyperplasia. Successful transplantation of some of these hepatomas has been made.

Support of cancer research in Holland was promoted by sending without expense to the government AxC strain rats for breeding stock, and rats inoculated with one of the above transplanted hepatomas to Dr. Swaen, R. K. University, Nijmegen, Holland.

Significance to Cancer Research: The difference in incidence of primary carcinoma of the liver between the sexes in man is well known. The predominance of primary liver cancer in human males varies from 2:1 in children to 6:1 in adults. The animal experiments described in this

No. 9 cont'd. NCI-344

project provide an experimental approach to the mechanism of carcinogenesis of the liver as influenced by sex and sex hormones. Furthermore, the liver being a biochemical factory whose ability to metabolize carcinogenic drugs under varying conditions such as provided by the sex differences noted above needs to be investigated to ascertain the extent its metabolism of carcinogens may be altered by sex and sex hormones.

Proposed Course of Project: The study of the intermediary metabolism of 2-diacetylaminofluorene is to be studied as soon as personnel are available. Arrangements were made for Dr. C. B. Clayson of Leeds University School of Medicine to come to Bethesda to start such studies but he has been unable to obtain a visa for health reasons. It is hoped he still may be able to start this project during the next year.

PROJECT REPORT FORM (CONT'D)

10. NCI-344

SERIAL NO.

11.

BUDGET ACTIVITY:

RESEARCH	[x]	ADMINISTRATION	[ ]
REVIEW AND APPROVAL	[ ]	TECHNICAL ASSISTANCE	[ ]

12.

COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 OR 1957

University of Kansas School of Medicine
Kansas City, Kansas

NO ENTRIES FOR ITEMS 13 AND 14.

15.

PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1955

Influence of sex and sex hormones on development of hepatomas and other hepatic lesions in strain AxC rats ingesting 2-diacetylaminofluorene. Harold P. Morris and Harlan I..Firminger. In press.

16.

HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1955.

None

PROJECT REPORT FORM

1. NCI 2. Laboratory of Biochemistry
INSTITUTE LABORATORY OR BRANCH

3. Nutrition and Carcinogenesis 4. - - - - - - - - 5. NCI-345
SECTION OR SERVICE LOCATION(IF OTHER THAN BETHESDA) SERIAL NO.

6. Hormonal factors involved in the induction of cancer of the liver in rats fed 2-di-acetylaminofluorene.
PROJECT TITLE

7. Harold P. Morris
PRINCIPAL INVESTIGATOR(S)

8. Harlan I. Firminger and Billie P. Wagner
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objective: To determine the influence of the hypopyhysis on the induction of liver cancer in rats ingesting the carcinogen 2-diacetylaminofluorene (2-diAAF).

Methods Employed: Nine groups totalling 160 F_1 hybrid male rats (produced from a mating of Buffalo females with AxC males) were used. The animals were divided into the following groups: normal controls without carcinogen and eight groups of 2-diAAF treated rats made up as follows: 1) normal, 2) castrated + testosterone, 3) castrated, 4) hypophysectomized, 5) sham hypophysectomized, 6) hypophysectomized and castrated, 7) hypophysectomized, castrated, and receiving testosterone, 8) hypophysectomized plus testosterone.

Groups of rats were fed a nutritionally excellent diet composed mostly of natural foods which was designed to keep the hypophysectomized rats alive for a long period in order to determine the effect of the treatment. This diet improved survival of the rats, but also delayed development of gross tumors. A second diet of lower nutritive value was used which resulted in shorter periods of survival.

Major Findings: The morphological studies have not been completed, but the gross evidence indicates that hypophysectomy either delays or inhibits the development of liver tumors by 2-diAAF.

Significance to Cancer Research: Hormonal factors may exert a profound influence on the development of liver cancer. These experiments were designed to produce additional experimental evidence on the basic mechanisms involved and once the experimental details of long survival have been solved the important role of hormones in the induction of cancer can be better elucidated and a procedure will be available for studies of the intermediary metabolism of a chemical carcinogen in which the conditions resulting in liver tumor formation can be altered.

No. 9 cont'd. NCI-345

Proposed Course of Project: It is hoped that the morphological material will be finished during the next year and that better techniques can be developed for keeping the hypophysectomized rats alive for longer periods.

PROJECT REPORT FORM (CONT'D)

10. NCI-345
SERIAL NO.

11.

BUDGET ACTIVITY:

RESEARCH	[x]	ADMINISTRATION	[ ]
REVIEW AND APPROVAL	[ ]	TECHNICAL ASSISTANCE	[ ]

12.

COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 or 1957.

University of Kansas School of Medicine
Kansas City, Kansas

NO ENTRIES FOR ITEMS 14, 15, AND 16.

PROJECT REPORT FORM

1. NCI 2. Laboratory of Biochemistry
INSTITUTE LABORATORY OR BRANCH

3. Nutrition and Carcinogenesis 4. - - - - - - - - 5. NCI-346
SECTION OR SERVICE LOCATION(IF OTHER THAN BETHESDA) SERIAL NO.

6. Liver function tests in rats receiving 2-diacetylaminofluorene
PROJECT TITLE

7. H. P. Morris
PRINCIPAL INVESTIGATOR(S)

8. Billie P. Wagner and L. S. Lombard
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objective: To devise a liver function test of sufficient sensitivity to detect functional changes in the liver prior to the development of recognizable morphological changes during the induction of cancer of the liver in rats fed a diet containing 2-diacetylaminofluorene.

Methods employed: The Taplin (A.E.C. Rpt. UCLA no. 319 1955) radioactive rose bengal liver function test was applied to AxC strain male rats receiving the carcinogen 2-diacetylaminofluorene. The radioactivity *in vivo* in the liver was measured by a collimated scintillation counter positioned directly over the liver area, the dye injected intravenously, and the I^{131} activity of the liver recorded continuously during a 60 minute period.

Major Findings: The functional tests of carcinogen-fed rats in comparison to controls showed progressive change with the length of time on the carcinogenic diet as follows: 1) radioactivity clearance rate decreased, beginning in the 4th week as the first indication of impared ability to eliminate the dye from the liver. 2) a delay in the uptake of radioactivity from the blood began to occur at the 6th week, 3) the total radioactivity uptake by the liver had diminished significantly after 6 and 8 weeks of ingestion of 2-diAMF, and little or no liver clearance took place. Morphologically there was a progressive increase in bile duct proliferation in carcinogen fed rats and essentially no change in controls. Carcinogen-fed rats at the 4th week showed a few areas suggestive of early neoplastic changes, while 6th and 8th week livers exhibited multiple frank hepatomas while control livers manifested no neoplastic changes.

Significance to Cancer Research: These experiments show impairment in the functional activity of the liver while the animal is being treated with a chemical causing the induction of liver tumors. This impairment in

No. 9 cont'd. NCI-346

functional activity can be detected before morphological changes, and while the test is not specific for detecting precancerous changes except under the specific conditions of the test they prove in this case that the functioning of the liver is impaired before recognizable morphological changes take place. The test might be useful in the early diagnosis of liver cancer in man especially in those areas where a high incidence of the disease is known to occur as in some parts of Africa.

Proposed course of project: It is planned to compare the liver functional test in rats receiving a few different carcinogenic chemicals and to study the influence of sex and other hormonal factors involved in the induction of liver cancer in rats.

PROJECT REPORT FORM (CONT'D)

10. NCI-346

SERIAL NO.

11. _____

BUDGET ACTIVITY:

RESEARCH	X	ADMINISTRATION	
REVIEW AND APPROVAL		TECHNICAL ASSISTANCE	

NO ENTRIES FOR ITEMS 12, 13, 14, 15, AND 16.

PROJECT REPORT FORM

1. NCI — INSTITUTE
2. Laboratory of Biochemistry — LABORATORY OR BRANCH
3. Nutrition and Carcinogenesis — SECTION OR SERVICE
4. ------- — LOCATION (IF OTHER THAN BETHESDA)
5. NCI-347 — SERIAL NO

6. Role of Tryptophan in the Induction of Bladder Tumors in Rats Ingesting 2-AAF
PROJECT TITLE

7. H. P. Morris
PRINCIPAL INVESTIGATOR(S)

8. B. P. Wagner, J. H. Weisburger, and H. M. Dyer
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objective: To determine the influence of either D- or L-tryptophan in the induction of a high incidence of bladder tumors in rats fed 2-acetylaminofluorene (2-AAF) and to provide animal material for intermediary metabolism of 2-AAF (Weisburgers) and the metabolism of tryptophan (Dyer) in rats receiving 2-AAF and D-, L-, or DL-tryptophan.

Methods Employed: Nine groups each comprised of 12 Buffalo strain female rats were started on tryptophan free diets containing 2-AAF with D-, DL-, or L-tryptophan and suitable controls. These animal experiments will require more than a year for completion since it appears that bladder tumors develop in rats after very long exposure to the carcinogen under the conditions of this experiment, therefore, no results have been obtained at this time.

Significance to Cancer Research: Bladder cancer is an occupational hazard to people employed in the dyestuffs industry. Aromatic amines are implicated in the carcinogenesis of bladder tumors in man. Animal experiments using 2-AAF and tryptophan are expected to help discover some of the factors involved in the origin of bladder tumors in rats.

Proposed Course of Project: Continuation of animal experiments now in progress.

PROJECT REPORT FORM (Cont'd)

10. NCI-347
SERIAL NO.

11.
BUDGET ACTIVITY

RESEARCH	[x]	ADMINISTRATION	[ ]
REVIEW AND APPROVAL	[ ]	TECHNICAL ASSISTANCE	[ ]

NO ENTRIES FOR ITEMS 12, 13, 14, 15, AND 16.

PROJECT REPORT FORM

1. NCI — INSTITUTE
2. Laboratory of Biochemistry — LABORATORY OR BRANCH
3. Nutrition and Carcinogenesis — SECTION OR SERVICE
4. — LOCATION (IF OTHER THAN BETHESDA)
5. NCI-348 — SERIAL NO

6. The Influence of the Thyroid Gland in the Development of Liver Cancer in the Rat
PROJECT TITLE

7. H. P. Morris
PRINCIPAL INVESTIGATOR(S)

8. B. P. Wagner and Pathology Laboratory, NCI
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objective: Preliminary experiments in our laboratory have shown that surgical thyroidectomy is completely effective in preventing the development of liver tumors in rats ingesting 2-diAAF.

Methods Employed: To determine the hormonal factors involved in this process of tumor induction, a large group of AxC strain male rats with and without surgical thyroidectomy will be studied under different dietary conditions, such as restricted feeding, use of desiccated thyroid powder, ad libitum feeding versus controlled administration of the carcinogen, etc. More than 100 rats will be used.

Major Findings: See above.

Significance to Cancer Research: The striking effect of surgical thyroidectomy in preventing the development of liver tumors in rats provides a new approach to the study of hormonal and nutritional factors involved in hepatocarcinogenesis by 2-AAF and related compounds. It is hoped such studies will more precisely outline some of the many factors involved.

Proposed Course of Project: The animal experiments will be started early in 1956. They will not only give valuable information on the role of the thyroid in the induction of liver cancer, but also provide information to guide metabolic studies (see J. B. Gilbert's report).

PROJECT REPORT FORM (Cont'd)

10. NCI-348
SERIAL NO.

11.
BUDGET ACTIVITY:

RESEARCH [x] ADMINISTRATION [ ]

REVIEW AND APPROVAL [ ] TECHNICAL ASSISTANCE [ ]

NO ENTRIES FOR ITEMS 12, 13, 14, 15, AND 16.

PROJECT REPORT FORM

1. NCI (INSTITUTE) 2. Laboratory of Biochemistry (LABORATORY OR BRANCH)

3. Nutrition and Carcinogenesis (SECTION OR SERVICE) 4. ---------- (LOCATION (IF OTHER THAN BETHESDA)) 5. NCI-349 (SERIAL NO)

6. Influence of Riboflavine on the Tumors Induced in Rats Ingesting 2-Acetylaminofluorene
PROJECT TITLE

7. H. P. Morris
PRINCIPAL INVESTIGATOR(S)

8. B. P. Wagner and C. A. Velat
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objective: To study the influence of different levels of riboflavine in the diet on the induction of several types of tumors by the non-organ-specific, distant acting carcinogen 2-acetylaminofluorene (2-AAF).

Methods Employed: Female Buffalo-strain rats were placed on high protein diets containing three different levels of riboflavine. They were given via stomach tube equal amounts of the carcinogen 2-AAF on a body weight basis. The carcinogen was administered in such a way that all the rats received equivalent amounts under identical conditions.

Major Findings: The data suggested that under the conditions of the experiment, riboflavine promoted the induction of mammary tumors, acoustic duct tumors, and a variety of tumors at other sites, but had no apparent effect on the incidence of liver tumors.

Significance to Cancer Research: The results obtained in this project give support to the concept that some dietary factors, such as riboflavine, have variable influences on the chemical induction of cancer and if this holds for other factors influencing chemical carcinogenesis, the problem of studying the mechanisms of carcinogenesis becomes much more complicated.

Proposed Course of Project: Some additional experiments may be planned and started in this area during the coming year.

PROJECT REPORT FORM (Cont'd)

10. NCI-349
SERIAL NO.

11.
BUDGET ACTIVITY:

RESEARCH [x] ADMINISTRATION [ ]

REVIEW AND APPROVAL [ ] TECHNICAL ASSISTANCE [ ]

NO ENTRIES FOR ITEMS 12, 13, AND 14.

15.
PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALEND YEAR 1955

1. H. P. Morris, B. P. Wagner, and C. A. Velat, Tumors Induced by 2-Acetylaminofluorene in Buffalo-strain Rats Ingesting Different Levels of Riboflavine. J. Nat. Cancer Inst., 16, 489 (1955).

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